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Discussion

MALIGNANT ADENOMA OF THE KIDNEY[1]

ROBIN PEARSE

From the Department of Urology, Toronto General Hospital, Toronto, Ontario, Canada

The following history is of a woman with a large adenoma of the kidney.

The patient, aged 58 years, was admitted to the hospital on January 24, 1947, complaining of gradually increasing weakness of 5 years duration. During this period she had lost 35 pounds. For the past 3 years she also had attacks of dyspnea accompanied by a pounding feeling in the heart, sudden in onset, subsidence gradual, and a sore red tongue.

Following one of the recent attacks of dyspnea the patient noticed a peculiar feeling in the left upper abdominal quadrant, and on examination her physician felt a mass, which he took to be a large kidney and referred her for investigation. Patient had no urinary symptoms.

Examination disclosed an afebrile, pale, thin woman with dark circles around the eyes, striae at the corners of the mouth and a bright red tongue with an irregular surface, heart slightly enlarged, blood pressure 140/80 and a pulmonary systolic murmur present.

A slightly tender movable mass could be felt in the left, upper abdominal quadrant, suggesting a moderately enlarged lower pole of the kidney.

The urine was negative; Wassermann negative; nonprotein nitrogen 29; hemoglobin 90 per cent; red blood cells 4.3; white blood cells 7.5; color index 1.05. Blood smears showed slight generalized macrocytosis, platelets plentiful.

Cystoscopy showed a normal bladder. Retrograde pyelograms showed a normal right kidney (fig. 1). On the left side the lower calyces were flattened and curved to the shape of an inverted saucer by pressure from a large spherical mass in the lower pole of the kidney (fig. 1).

A tentative diagnosis of parenchymal carcinoma was made and the patient prepared for transperitoneal nephrectomy. In the interim the sore tongue and oral striae disappeared following intramuscular injections of vitamin B complex.

Operation: Anesthetic, spinal nupercaine. The abdomen was opened by an incision through the mesial third of the left rectus muscle, extending from just above the costal cartilage down to the level of the umbilicus. The descending colon was retracted to the right and the posterior peritoneum opened along the white line. The anterior layer of the perirenal fascia was torn through and the tissues retracted to the midline. This exposed a large tumor in the lower pole of the kidney. The ureter, which was very small, was divided. A large artery entered the upper pole of the kidney. The renal vein was very large and beneath it could be felt a small artery. After dealing with the blood supply, the kidney was removed, the posterior peritoneum repaired and the abdomen closed; peritoneum, muscle and fascia united by a series of figure of eight wire sutures and the skin by continuous dermal.

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

The patient made an uneventful recovery and went home on the fifth post-operative day.

Pathological report (W. L. Robinson): The kidney measured 14 by 12 by 8 cm. (fig. 2). The external surface was pale brown in color, and there was a

FIG. 1. Urogram

FIG. 2. Hemisection of kidney

marked enlargement of the lower pole so that the lower four-fifths of the kidney was spherical in shape. This sphere measured 12 cm. in diameter. On opening the kidney a large encapsulated mass was seen, measuring 10 by 7 cm. The mass was situated mainly in the lower and central portions of the kidney. There

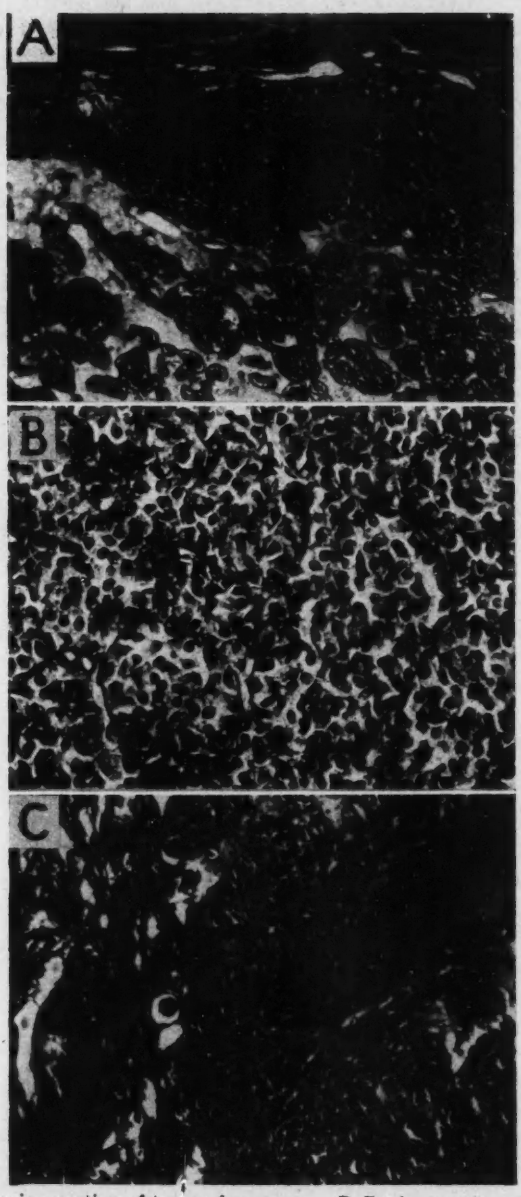

FIG 3. *A*, Benign portion of tumor, low power. *B*, Benign portion of tumor, high power. *C*, Malignant portion of tumor

was a small piece of normal kidney at the lower pole and a somewhat larger piece of normal tissue at the upper pole.

The tumor itself had a central, very firm, gray-white area, which spread in a dendroid manner into the surrounding tumor tissue. This surrounding tumor tissue was brownish red in color, in many places resembling normal kidney tissue. Except for a few submucous hemorrhages, the pelvis was normal. The ureter was extremely narrow.

The tumor presented the histological features of a solid type of adenoma. It had a definite fibrous tissue capsule. The component cells, for the most part, were uniform in size and shape, and possessed a moderate amount of pink-staining cytoplasm with compact, dark-staining nuclei. In some areas the cells had a tendency to form acini but, for the most part, they were growing in solid cords separated by a delicate connective tissue framework. In the center of the tumor were degenerative changes comparable to those frequently seen in thyroid adenomata, such as atrophy of the epithelial elements and replacement by a very loose-textured connective tissue stroma with, here and there, small areas of hemorrhage.

The tumor showed certain malignant characteristics, in local invasion of its own capsule, and areas where the cells were quite atypical in character, as indicated by variation in their size, shape and nuclear staining qualities. See figure 3.

EXTENSIVE METASTASIZING HYPERNEPHROMA ASSOCIATED WITH MASSIVE BILATERAL ADENOMA OF THE ADRENAL[1]

JOHN A. TAYLOR

The subjects of bilateral adrenal adenoma and hypernephroma per se have been well discussed and little of interest can be added. The association of the three lesions in a single case, with a diagnostic problem, together with added data in connection with the Grawitz theory of adrenal rests is worthy of consideration.

Howze, in a report of a case of bilateral adrenal adenoma with a review of the literature in 1942, found 66 cases. In all of these cases but one, the tumors were found at autopsy. The same was true in this case, it being one of the asymptomatic cases described by Cahill in his presentation of adrenal tumors.

The most interesting phase of this case was the circumscribed tumor contiguous with the right adrenal adenoma. This tumor was soft and reddish gray in color, and friable, in contrast to the yellow, firm, cortical tumor. Microscopically, it was composed of large clear cells which could have arisen from renal parenchyma or an adrenal rest. It is typical of hypernephroma. Whatever its origin, we are dealing here with a so-called hypernephroma growing side by side with massive adrenal hyperplasia.

CASE REPORT

A 54 year old male was admitted to the Hospital for Special Surgery on September 13, 1943. He had no complaints until he fell while working 10 weeks before. This injury proved to be irrelevant. Pain developed in the left buttock, radiating down the leg. He had been treated in another hospital for sciatica with diathermy, massage and rest, without benefit, and was transferred because of increasing pain and disability.

There was marked limitation of the motion in the left hip. There was a lump over the sixth rib. The pain was relieved somewhat by traction. Blood count showed 4,000,000 red blood cells with 80 per cent hemoglobin, 9,300 leucocytes with 70 per cent polymorphonuclears. The Kline test was negative.

The blood sedimentation rate was 90 mm in 1 hour.

Blood studies (E. R. Gutman): Serum alkaline phosphatase 4.7 Bodansky units. Acid phosphatase 3.8 G. units per cent. Inorganic P 4.0 mg per cent; calcium 16.2 mg per cent; protein 5.7 per cent.

X-rays (fig. 1) showed extensive destructive changes seen in the left ilium, in the right sacral wings; and there were probably destructive changes in several of the vertebral bodies, notably the seventh and twelfth dorsal and the second lumbar. There was considerable collapse of the seventh dorsal body. Destructive and productive changes were seen in the sixth left posterior rib. The find-

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

ings were characteristic of multiple carcinoma metastases. Examination of the skull, shoulders, and of the ribs, gave no further evidence of metastasis.

A genito-urinary consultation was asked to rule out prostatic cancer. The prostate was not suggestive of malignancy and hypernephroma was considered, although the kidneys were not enlarged to palpation. Cystoscopic studies were precluded because of the extensive vertebral involvement with paraplegia which had developed.

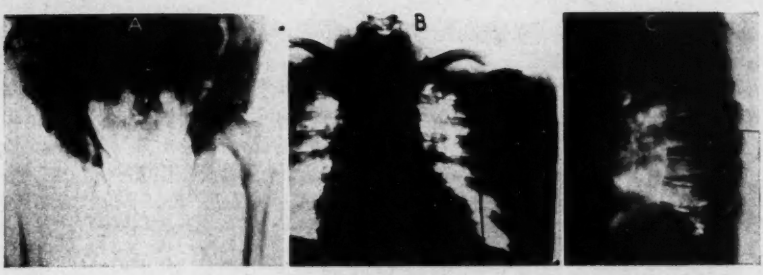

FIG. 1. *A*, Showing destructive changes in left ilium. *B*, Showing destructive and productive changes in sixth rib. *C*, Showing collapse of seventh dorsal vertebra.

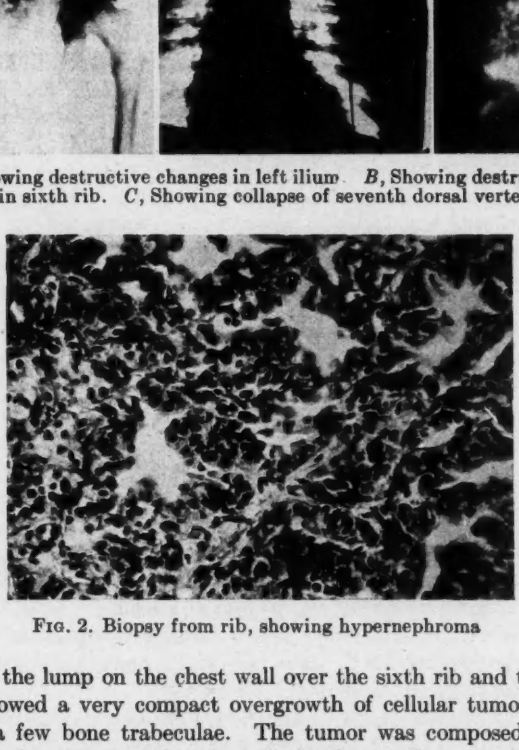

FIG. 2. Biopsy from rib, showing hypernephroma

A biopsy of the lump on the chest wall over the sixth rib and the pathologic study of it showed a very compact overgrowth of cellular tumor tissue interspersed with a few bone trabeculae. The tumor was composed of glandular epithelial cells forming complex, but distinctly papillary structures. These papillae were supported on delicate compressed strands of connective tissue stroma. The tumor cells were characterized by a clear vacuolated cytoplasm and a relatively small vesicular nucleus. The type of cell and papillary pattern suggested strongly that the tumor had originated in the kidney (fig. 2). Diagnosis: Metastatic papillary carcinoma. The probable primary site of the tumor is a hypernephroma or clear celled carcinoma of the kidney.

The patient grew rapidly worse and died on October 10, 1943.

Autopsy (Dr. Milton Helpern): "The body is that of a heavy set middle aged white man, 65 inches tall, estimated weight about 170 pounds. There is moderate obesity of the trunk and abdomen. Scalp hair is black; the eyes are brown; there are several missing teeth. There is purplish postmortem lividity posteriorly. Genitalia appear normal; foreskin present. There is a small granulating surgical incision on the right anterior chest wall 2.5 inches in length. The medial 1 inch of this incision is healed and situated 2 inches about and 1 inch medial to the right nipple. There is moderate swelling of the left thigh with slight shortening and external rotation. There is an area of decutitus on the upper lateral surface of the right thigh. The autopsy was performed through an abdominal incision.

"On section of the trunk, the panniculus is 1 to 2 inches in thickness. The recti muscles are not unusual. The diaphragm on the right is at the level of the fourth rib and on the left at the level of the fourth interspace. The peritoneum is everywhere smooth and shiny except for some fibrous thickening and induration over the descending colon just below the splenic flexure, where a segment of the bowel is found to contain many variable sized inflamed diverticula. These are imbedded in some indurated fat tissue. The liver is slightly enlarged and projects a finger breadth below the right costal margin.

"On opening into the chest, the lungs are found to lie free in the pleural cavities which contain no fluid. No evidence of embolism is found in the pulmonary vessels. The lungs are large, voluminous and heavy. They are crepitant throughout. On section there is considerable edema of the lung parenchyma and also congestion in the dependent portions. The bronchi are not obstructed. They are somewhat thickened and the mucosa is congested. In the visceral pleura of each lung there are several small pearly-gray thin plaques from $\frac{1}{8}$ to $\frac{1}{4}$ of an inch in diameter. There are no metastases in the lung parenchyma.

"The heart lies free in the pericardial sac and weighs 440 gm. There is moderate hypertrophy of the large ventricle; there is also an excess of sub-epicardial fat. The chambers of the heart contain abundant postmortem "chicken fat" clot. The pulmonic valve, instead of being divided into 3 equal sized cusps contains 1 cusp which is subdivided into 2 of unequal size, one considerably larger than the other. The mitral valve leaflets are slightly thickened and the ring calcified. The aortic valve cusps show moderate fusion of the commissures. The tricuspid ring is $4\frac{3}{4}$ inches and the pulmonic ring $3\frac{3}{8}$ inches in circumference; the mitral ring is $4\frac{1}{4}$ and the aortic ring is 3 inches in circum erence. The left ventricle is $\frac{3}{4}$ inch in thickness. The coronary arteries are patent at their mouths and throughout their course show a moderate amount of eccentric atherosclerosis.

"The myocardium, in section, is brown in color without fibrosis. The aorta throughout its length is somewhat inelastic and in the abdominal portion there are a few calcified plaques.

"The esophagus is natural. In the cardiac end of the stomach, the mucosa is hyperemic. The stomach contains some greenish gray mushy content. The small bowel contains some mushy greenish brown content and the large bowel

some mushy greenish brown feces. In the descending colon just below the splenic flexure there is a segment of bowel 3 inches in length which is indurated. On section of this segment of bowel there are several diverticula, the largest of which is 2.5 cm. in diameter. This diverticulum shows evidence of chronic inflammation and is firmly adherent to the surrounding pericolic fat which is also indurated. It is filled with a semiliquid fecal material. The remainder of the large bowel is not unusual. The appendix is present.

"The liver is slightly enlarged, normal in configuration. On section it is reddish brown in color. It contains several small discrete tumor metastases which

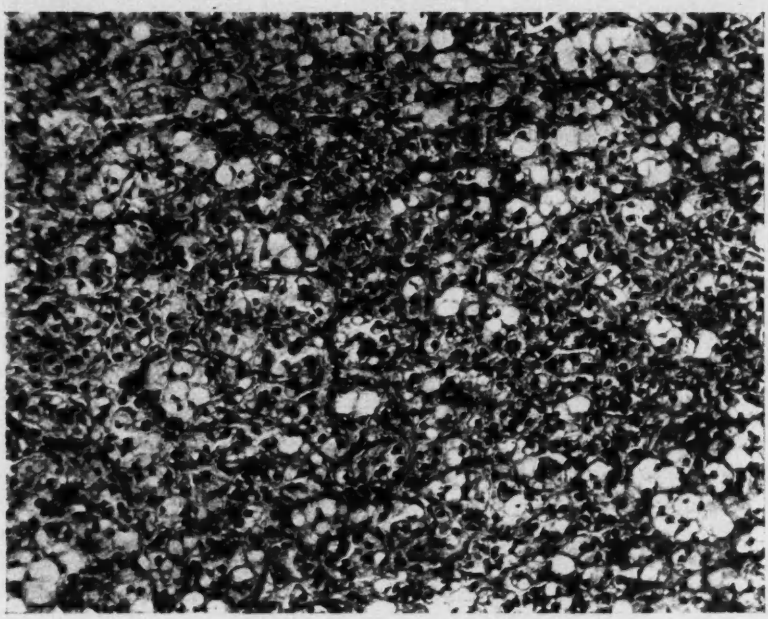

FIG. 3. Metastases in liver

are gray in color. One of these is seen on the superior surface of the right lobe and another one is found on the posterior surface of the right lobe. These metastases are 1 cm. in diameter. See figure 3.

"The gallbladder contains a few cubic centimeters of green bile. There are no stones. The bile ducts are not obstructed.

"The pancreas is normal.

"The spleen is slightly enlarged and soft in consistency. On section, the pulp is red in color. The follicles are indistinct.

"Both adrenals are considerably enlarged and replaced by golden yellow cortical tumor tissue (fig. 4). On each side the adrenals form firm, nodulated broad, thick masses of tumor surrounded by a considerable amount of fat. On the left side, the adrenal measures 11 by 4 by 2.5 cm. On the right side, the solid nodu-

lar tumor replacing the adrenal is 10 by 4 by 3 cm. Both adrenal tumors are entirely discrete and separate from the kidneys.

"The kidneys are imbedded in large fatty capsules. The left kidney is normal in size measuring 13 by 6 by 4 cm. The fibrous capsule strips easily. The mark-

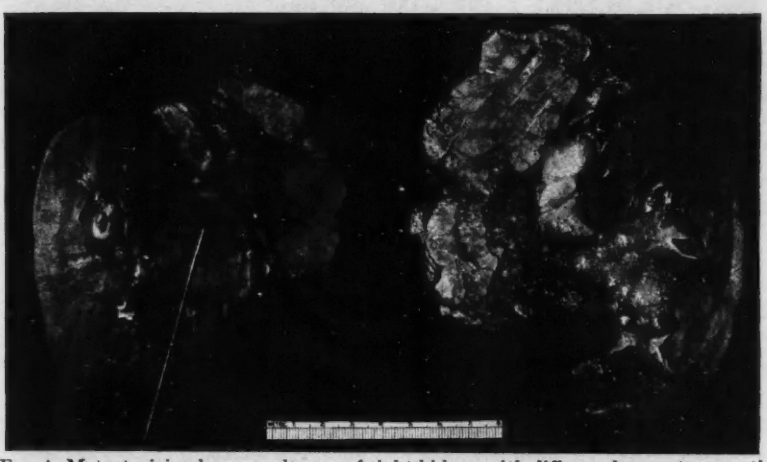

FIG. 4. Metastasizing hypernephroma of right kidney with diffuse adenomatous cortica hyperplasia of both right and left adrenals.

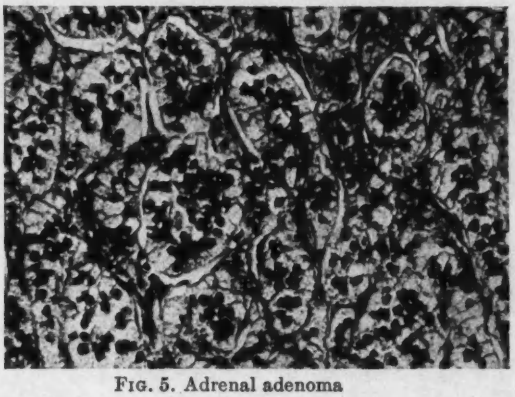

FIG. 5. Adrenal adenoma

ings are somewhat exaggerated. The pelvis and ureter are normal. The right kidney is also imbedded in a large amount of perirenal fat and is 12 by 5 by 4 cm. There is a circumscribed tumor projecting from the hilum of the right kidney and situated more in the lower half. This projecting tumor appears to be encapsulated and measures 4.5 by 2.5. On section, this tumor is lobulated and trabeculated, the lobulations varying from 1 to 2.2 cm. in diameter. The tumor tissue, on section, is soft and pinkish and reddish gray in color. It is very

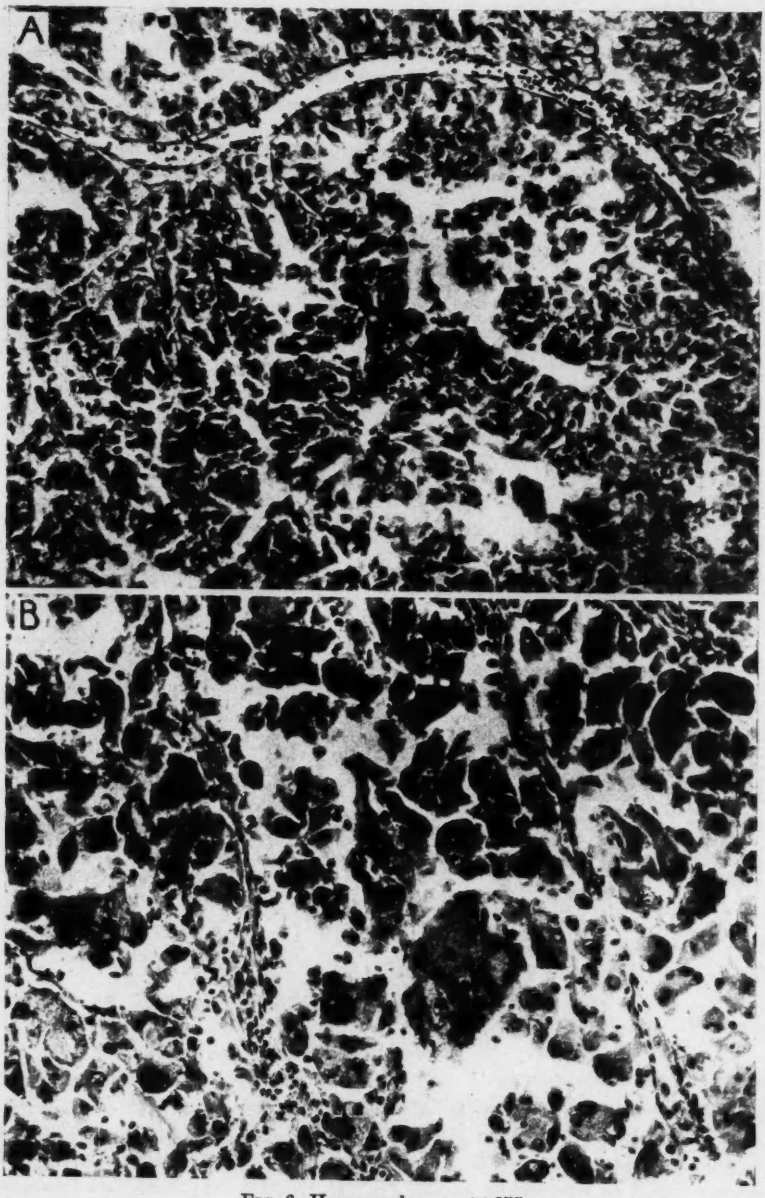

FIG. 6. Hypernephroma, × 375

friable in consistency in contrast to the golden yellow, firm cortical tumors of both adrenals. Grossly there is no evidence of invasion of the surrounding

renal veins. The pelvis and ureter of the right kidney do not contain any blood and the markings of the kidney parenchyma are fairly well preserved. See figures 5 and 6.

"The urinary bladder is hypertrophied and the bladder wall is trabeculated. The bladder contains 4 oz. of turbid yellow urine.

"The lateral lobes of the prostate show nodular hypertrophy. The seminal vesicles are normal. The testicles are normal.

"Examination of the left acetabulum reveals complete replacement of that bony structure by soft metastatic tumor tissue, which has completely destroyed and replaced it. The tumor mass is 3 inches in diameter and is readily excised with a knife. When this mass of soft tumor is removed the head of the femur can be palpated through the large defect in the bone. The psoas muscles are atrophied.

"The head is not examined.

"Cause of death: Hypernephroma of the right kidney with skeletal metastases.

"Anatomical diagnosis: Hypernephroma of the right kidney with metastases to ribs (surgical biopsy), left acetabulum and liver; bilateral large cortical adenomata of the adrenals; pulmonary congestion and edema; moderate hypertrophy of the left cardiac ventricle; moderate coronary arteriosclerosis; sclerosis of mitral valve; anomaly of pulmonic valve (4 cusps), atherosclerosis of aorta; diverticulitis coli; recent right headed rib biopsy incision."

SUMMARY

A case of bilateral adrenal adenoma associated with a small clear cell carcinoma which metastasized extensively and caused death is herewith presented.

The writer is indebted to Dr. Francis Carter Wood for the microphotographs.

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OSTEOGENIC SARCOMA INVOLVING THE RIGHT KIDNEY[1]

H. G. HAMER AND WM. NILES WISHARD, JR.

A number of extraskeletal ossifying tumors have been reported in the literature, but involvment of the kidney was rare and the incidence of osteogenic sarcoma involving the kidney extremely rare. Harwell Wilson reviewed from the literature 30 cases of bone forming malignant tumors in soft parts, the histological reports in the most of them being compatible with true osteogenic sarcoma. This group included: thyroid, 6; nipple, 1; gallbladder, 1; chest wall, 1; breast, 10; calcified hematoma, 1; abdominal wall, 1; kidney, 1; vastus externus, 1; mesentery, 1; soft tissue of the thigh, 3; and fascial plane of the calf, 1. Wilson mentions Sein Alpers' report of an osteochondroma arising from the dura and citation of 2 cases by other authors of similar tumors; also Dunning, Curtis and Bullock's report of 2 cases of osteogenic sarcomata of soft tissues caused by injecting benzopyrine subcutaneously into a group of 842 rats.

Stier and Lyman reported a case of osteoblastic sarcoma of the uterus. Tremblay, Crane and Harris reported a case of primary osteogenic sarcoma of the bladder and reviewed 8 cases of bone and cartilage forming tumors of the bladder. Henry Morris quotes Roberts that "a fibrous tumor growing in the substance of the kidney may ossify and transform a large part of the organ into a bony mass. The fibrous capsule of the kidney has also been known to undergo ossification, as in the historical specimen which Elliston sent to Royer of two ossified renal capsules taken from a man who died with symptoms of apoplexy."

Newman points out that many so-called bony growths are in reality calcified inflammatory products. Dickinson states: "There are many preparations in museums which show formations within the kidney of bony hardness; these appear to be usually derived from the transformation of hydatids; and he refers to specimens in the museums of Guy's and the Royal College of Surgeons in support of his statement."

Roberts, referring to changes which take place in pyelitis and pyonephrosis says "sometimes fibrous septa which separate the compartments are extensively calcified. In an example of this kind which was handed me for examination, a saw was required to cut the kidney across, and a piece of one of the bony septa which was ground down, displayed under the microscope the character of true bone, though in a rudimentary state. A fine specimen of similar transformation is preserved in the museum of Owens College. Cartilaginous growths are still less frequent than bony. Gluge, however, speaks of a growth apparently consisting mainly of cartilage in a hydronephrotic kidney, and there is in the Archives of Pathological Anatomy, 1886, a note of a chondro-sarcoma having been recorded by Hoisholt of San Francisco." George Austin, Jr. in a paper entitled "Calcification of Renal Tumors," reviewed 98 verified malignant tumors of the kidney. In one instance true bone formation was seen about the periphery of

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

a large mass of necrotic material. Keyes in discussing the pathogenesis of hypernephroma, says "the tumor usually remains quiescent from 45 to 60 years. It may then grow so slowly that a marked desmoplastic reaction is set up in the kidney about it, and the process may go on to complete calcification in the capsule of the tumor. We have seen such a tumor, the capsule of which was so hard as to require the use of a skull saw for its division."

Thevenot, in a treatise on perinephritic tumors, illustrates a case of osteoma of the fibrous capsule of the kidney as observed by Marion. In discussing connective tissue tumors he states: "They are infrequent and that they have origin in the fibrous capsule or the fatty capsule. The first are fibromas and sarcomas. The second offer a much greater variety." Marion, under the heading of osteoma of the kidney, states that "these are rare," and refers to 4 cases; one a personal case, and one of Desnos. In his comment he says "these present themselves as a round tumor making a bulging or swelling under the capsule of the kidney from which they arise, and they are composed of osseous tissue."

Kretschmer reported a case of retroperitoneal pararenal osteoma in a woman aged 63. His article included an extensive review of the literature on heteroplastic bone formation. Weber reported a case (female, aged 15) of osteochondrosarcoma enclosing the left kidney and suprarenal gland. Haining and Poole, under the title "Osteoblastoma of the Kidney, Histologically Identical With Osteogenic Sarcoma," reported a case (male, aged 76) of osteogenic sarcoma of the left kidney with metastasis to the right kidney, liver and bowel. These 2 latter cases are the only cases of osteogenic sarcoma of the kidney found in a search of the literature.

CASE REPORT

Mr. J. W. N., aged 76, was admitted to the Methodist Hospital March 7, 1944, because of frequency of urination and hematuria. The former symptom had been present for 3 or 4 months, and the hematuria for 2 days. The patient had been well until 4 years previously when he had an attack of gastro-intestinal disturbance with intestinal hemorrhage. X-ray examination at that time had disclosed the presence of stomach ulcer. The family history was negative for diabetes, tuberculosis and malignancy. Upon admission to the hospital he was passing bloody urine at frequent intervals. His temperature was 100.4; pulse 62; respiration 18, blood pressure 148/70. Abdominal palpation detected a tumor mass in the right upper abdomen. Rectal palpation disclosed grade 2 benign hypertrophy of the prostate. By catheterization 1½ ounces of residual urine was obtained. The blood findings were as follows; hemoglobin 91 per cent, (14 gm.); red blood cells 4,590,000; white blood cells 7,600; polynuclears 84; small lymphocytes 16. The phenolsulphonphthalein output was 43 per cent for 2 hours. Cystoscopy disclosed a bladder of normal capacity with slight trabeculation of the walls and median and lateral lobe hypertrophy of the prostate. The ureters were catheterized easily. Bloody residual urine (35 cc) was aspirated from the right kidney pelvis. The urine from the left kidney was clear, and the urine from each kidney contained an occasional pus cell. An original

roentgenogram showed an egg shaped shadow in the region of the upper pole of the right kidney about 4 by 8 cm. in size with smaller areas of calcification situated above and slightly lateral to it. (fig. 1, *A*) The left pyelogram was normal, while the right pyelogram showed the pelvis to be displaced laterally and some what dilated (fig. 1, *B*). Examination of the colon by barium enema revealed no evidence of organic lesion of the colon or terminal ileum. The hepatic flexure of the colon was slightly displaced downward and anteriorly. A film of the chest showed the bony thoracic cage to be normal. The heart was within normal limits of size. The aorta was slightly tortuous but not dilated, and showed arteriosclerotic changes. Both domes of the diaphragm were smooth and the angles clear. The pulmonary parenchyma was clear with no evidence

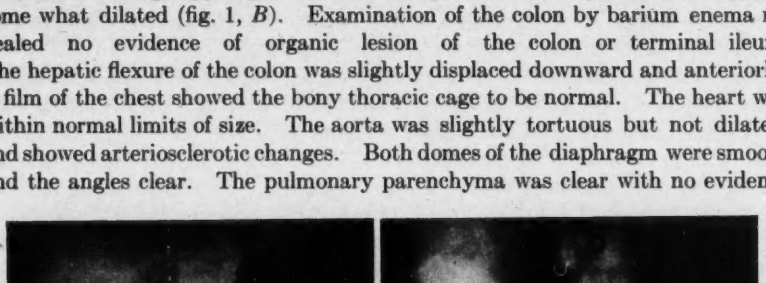

FIG. 1. *A*, Anteroposterior view, showing a dense shadow in region of right kidney. *B*, Pyelogram, showing compression of kidney and distortion of pelvis.

of metastasis. There was slight bilateral apical pleural thickening. Under bed rest the hematuria readily subsided and the patient's general condition was sufficiently improved that he was allowed to go home on March 10, 1944 (after 3 days in the hospital). The presumptive diagnosis was hypernephroma of the right kidney with calcification. Surgical interference was considered but was held in abeyance.

On March 15, 1944, upon recurrence of the hematuria, the patient was readmitted to the hospital for irradiation of the tumor mass in the right upper quadrant in the hope of controlling the hemorrhage. These treatments were tolerated badly and were accompanied by progressive weakenss. He began having bloody stools. These persisted and the patient gradually became weaker, more depressed and pessimistic. The blood examination made April 3, 1944 disclosed the following: hemoglobin 52 per cent (8 gm.); red blood cells 2,460,000; white blood cells 4,900; polymorphonuclears 96; small lymphocytes 3. The

nonprotein nitrogen was 51 mg. per 100 cc of blood. He was given transfusions of whole blood, 500 cc each, on March 31, April 3 and April 6. Repeated bowel movements during the night of April 5 contained a considerable amount of bright red blood, and the patient died in the midforenoon of April 6, 1944. The immediate cause of death was hemorrhage.

Autopsy: The body was that of a white male 5 feet 8 inches in height and estimated weight of 130 pounds, with slight evidence of senile atrophy of body development. No anomalies or deformities, signs of trauma or surgical wounds were present. The extremities were symmetrical with no evidence of bony or muscular disease. There was a small encrusted ulcer on the anterior aspect of the right lower leg.

An ulcerated tumor mass 4 cm. in diameter was present, situated just proximal to the pylorus on the posterior gastric wall, quite firm of texture and adherent to the head of the pancreas. Just proximal to the larger tumor were smaller ulcers, each 2 cc in diameter. These were on the lesser curvature of the stomach and were not indurated. There was no obstruction present but the stomach was slightly distended with grumous black fluid, but no fresh blood. The remainder of the gastro-intestinal tract revealed no pathological change of significance.

The head of the pancreas was indurated and adherent to the stomach, as previously mentioned, but was apparently free from tumor. The remainder of the pancreas was not remarkable.

The pleura were smooth and there were a few adhesions present in various parts of each lung. There was approximately 100 cc of clear straw colored fluid in each pleural space. The right lung weighed 660 gm., the left 480 gm. Both lungs showed a small amount of congestion of the lower lobes, but this was not particularly striking. The lungs for the most part were air bearing throughout. A few tumor nodules were found just beneath the pleura. The largest of these measured about 1 cm. in diameter. They were very firm and apparently metastatic.

The liver was considerably increased in size, the edges were rolled. On section there was considerable congestion present. There was no evidence of cyst or infarction, but scattered throughout the liver, particularly in the tissue beneath the capsule, were numerous small areas of tumor, apparently metastatic. The largest was about 1 cm. in diameter.

The gallbladder was of average size and shape. It was free from distention, and there was very little thickening of its walls. There were no stones present, and the biliary tract was found to be patent throughout.

No notable lymph glands were found in the abdomen.

The urinary bladder was not distended. The wall was of average thickness and was free from inflammation. The prostate was slightly enlarged but not indurated. The urethra was patent.

The left kidney was in the usual location and was surrounded by a slightly increased amount of perirenal fat. It weighed 140 gm. On section it was paler than usual and the striations were considerably diminished. There were no evidences of infarctions, cysts or tumors. The capsule was rather adherent and

the kidney surface was slightly granular. The pelvis and ureter were not remarkable. The left adrenal showed no gross abnormality.

The right kidney was encased in a large amount of fat (fig. 2); at the lower pole and slightly lateral to it was a tumor suggestive of lipoma, measuring about 10 cm. in diameter. The remainder of the kidney contained a large, firm tumor mass. The ureter and renal vessels disclosed no abnormalities. Upon longitudinal section of the kidney and tumor, a very hard mass was encountered. This could not be cut with a knife. It was cut partially across with a saw, but in some areas the tumor was so firm that the saw would not cut it and it had to

FIG. 2. Showing kidney and bony tumor. *A*, Bony tumor; *B*, fat; *C*, compressed rena parenchyma.

be separated with a chisel. Upon completion of the dissection it was apparent that the tumor arose in the supportive tissue posterior to the superior pole of the kidney and had grown into the kidney and inverted the kidney pelvis, but had not distinctly invaded it. Part of the tumor had a rather pale appearance suggestive of liposarcoma. Other parts resembled normal red bone marrow, while other parts consisted of hard, eburnated bone which was almost stony in consistency. The entire mass measured about 15 cm. across; weight 2010 gm. The kidney substance was considerably distorted and largely destroyed, there being only scant remaining normal architecture. The right adrenal could not be identified.

Microscopic examination: There was no section showing the capsule of the right kidney. The glomeruli seemed to be normal in number and fairly uni-

form in size and shape, the tufts filling the capsular apices. Several glumeruli were completely hyalinized, and all showed some round cell infiltration, not dense but suggesting an inflammatory process. The proximal convoluted tubules appeared to be fairly normal but the distal convoluted tubules and collecting tubules showed cloudy swelling and the interstitial tissues dense collections of inflammatory cells. The blood vessels throughout the section showed thickening of the walls and in some, almost complete obliteration of the lumen.

Sections from the large bony tumor (fig. 3) showed atypical bone spicules which formed no definite pattern. The osteoblasts were aligned on the edge of the spicules in an irregular fashion and not at all orderly as in normal bone. The sections were typical of osteogenic sarcoma of the sclerosing type.

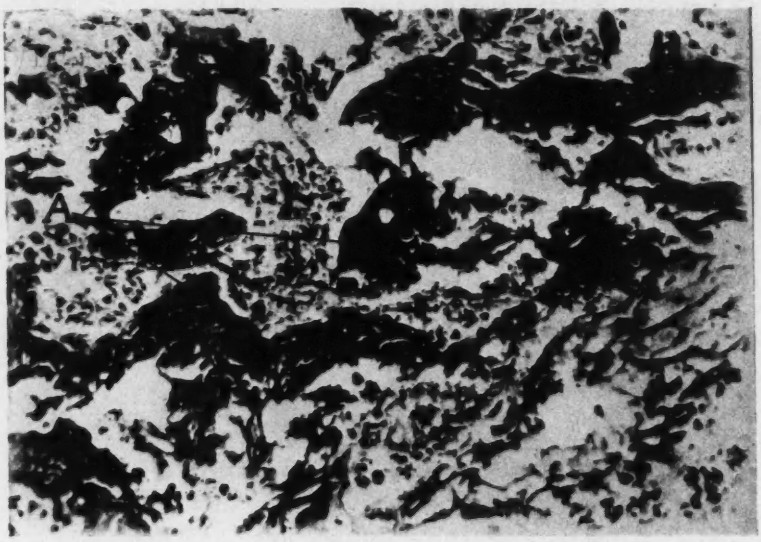

FIG. 3. Section through bony tumor. *A*, Spicules of bone

Sections through the stomach showed an ulcer crater which had eroded to within a few millimeters of the pancreatic tissue. There was no evidence of carcinoma in the stomach tissue.

Sections through the liver showed the capsule slightly increased in thickness. Beneath the capsule and scattered throughout the liver, especially in the portal areas, there were areas of dense round cell infiltration, in some instances completely outside the bounds of the portal triads. There was no evidence in the liver of metastasis although reported in the gross examination.

Sections through the lungs showed congestion and a moderate amount of emphysema. There were numerous areas in the lung in which there was definite bone formation and osteoid tissue, the pattern of the bone being essentially the same as that seen in sections from the tumor of the kidney (fig. 4).

Sections from the left kidney, the spleen and the pancreas showed no evidence of malignancy.

While nodules were found in the liver on gross examination, no evidence of metastasis was found microscopically. There was no evidence of malignancy found in the stomach tissue. The gross specimen was reviewed and it is apparent that that tissue which was mistaken for malignant tissue was granulation tissue from the edge of the ulcer. Conclusions: Osteogenic sarcoma of right kidney with metastasis to the lungs; ulcer of the stomach.

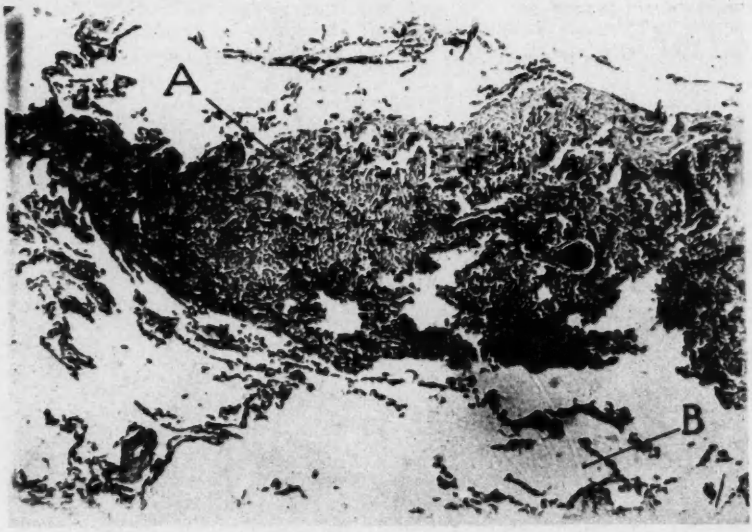

FIG. 4. Section of metastatic tumor of lung. *A*, Metastatic tumor. *B*, Lung

THEORIES OF BONE FORMATION IN SOFT TISSUES

Woolley states that there are three hypotheses to account for the heteroplastic bone formation:

1. Occurrence of embryonic "rests" of osteogenic tissue—misplaced during development—which in later years, due to changed physiological conditions, commence to grow and produce bone.

2. Transference of osteoblasts by the blood stream to unusual locations.

3. Metaplasia doctrine—any cell may, within certain tentative conditions, change its morphological features and become physically and chemically similar to other cells arising from the same general layer. Woolley favors the latter theory.

Mallory also supports the theory of metaplasia.

Hansman and Budd consider bone formation quite within the potency of the mesenchymal cells and do not consider them metaplastic.

Virchow believed that all bone and cartilage arose from fibroblasts by metaplasia.

To Leriche and Policard the fibrous tissue, cartilage and bone are all end products of a common mesoblastic stem. This does not mean that they may directly interchange identities, but under certain conditions they may revert or dedifferentiate into an embryonic state and when this occurs fibroblasts may become osteoblasts and form true bone. This theory upsets none of the facts and offers a reasonable explanation of normal and abnormal formation of bone.

SUMMARY

A case of osteogenic sarcoma of the kidney is reported.

In a review of the literature on kidney tumors several cases of bone formation within the kidney were found but only 2 cases of osteogenic sarcoma.

Of the cases found in the literature one was a man of 76 and the other a child (female) of 15. Our case was 76 years of age.

Rapid development of this ossifying tumor is indicated by a negative x-ray 5 years prior to his death.

Weber's case had sarcoma of the lower femur and of the kidney, identical in structure, and he was unable to decide which was primary. Haining and Poole's case had metastasized to the other kidney. Our case had metastasized to the lung.

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A MIXED TUMOR OF THE KIDNEY LIPO-MYO-HEMANGIOMA[1]

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Benign tumors of the kidney usually produce very few symptoms unless they attain considerable size, and then the symptoms are usually those of pressure. Exceptions to this rule are hemangiomata and papillomata of the renal pelvis. These two types of tumors may produce such severe hematuria that prompt nephrectomy is necessary. The following case report is unusual in the onset of the symptoms, the gross appearance of the tumor, and the histological pattern of the neoplasm.

Mrs. A. B., a housewife, aged 47, entered the Presbyterian Hospital on August 18, 1946, because of an acute attack of sharp pain in the left costovertebral region of 6 weeks' duration. The pain had occurred suddenly, did not radiate, and could be relieved by the application of heat. During the following 3 weeks, the character of the pain changed to a constant dull ache. There had been no other symptom. The urine had never been bloody. She had always been in good health until 1 year previously, at which time a fibroid was removed from the uterus. She had made an uneventful recovery from this operation. Her weight had not varied in the preceding 5 years.

Physical examination on admission to the hospital revealed a well-nourished and healthy appearing woman about 45 years of age. The temperature was 99.0° and the blood pressure was 112/70. The head, neck, chest, and heart were within normal limits. No masses were palpable in the abdomen. Neither kidney could be felt. However, tenderness could be elicited on bimanual palpation of the left costovertebral region. There was no inguinal adenopathy. The extremities and superficial reflexes were normal. The hemoglobin was 13.9 gm. per 100 cc of blood; red blood cells 4,300,000; white blood cells 7100 per cu. mm. Urinalyses were negative on two separate occasions. Cultures proved the urine to be sterile. X-ray films of the chest were normal with clear diaphragm shadows. However, the plain x-ray film of the genito-urinary tract revealed the left kidney outline to be enlarged. Excretory pyelograms revealed a marked dilatation of the upper minor calyx, with some distortion of the upper and middle major calyces of the left kidney. The right pyelogram was normal. A left retrograde pyelogram (fig. 1,*A*) which was made several days later, confirmed the changes seen in the excretory pyelograms. Cystoscopic examination revealed a normal bladder.

From the above evidence the diagnosis of a left renal tumor was made. A left nephrectomy was performed through a left loin incision 4 days after the patient entered the hospital. No difficulty was encountered in removing the kidney. Examination of the tumor at the time of operation showed it to have all the gross

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

characteristics of a hypernephroma. The postoperative course was uneventful and the patient left the hospital 11 days after the operation. She has since returned to the out-patient department several times. Her last visit was in April 1947, at which time her health was very good.

The gross specimen measured 11 by 6.5 by 3.5 cm. and weighed 290 gm. (fig 1., *B*). It was surrounded by adherent perirenal fat. On one surface of the specimen was a tumor 8 by 4 by 4 cm., firmly imbedded in the kidney. On another surface was a previously opened area of cystic degeneration lined by necrotic, hemorrhagic, neoplastic tissue. This cyst was approximately 4 cm. in diameter. Between the cyst and the renal parenchyma was a solid neoplastic mass. The

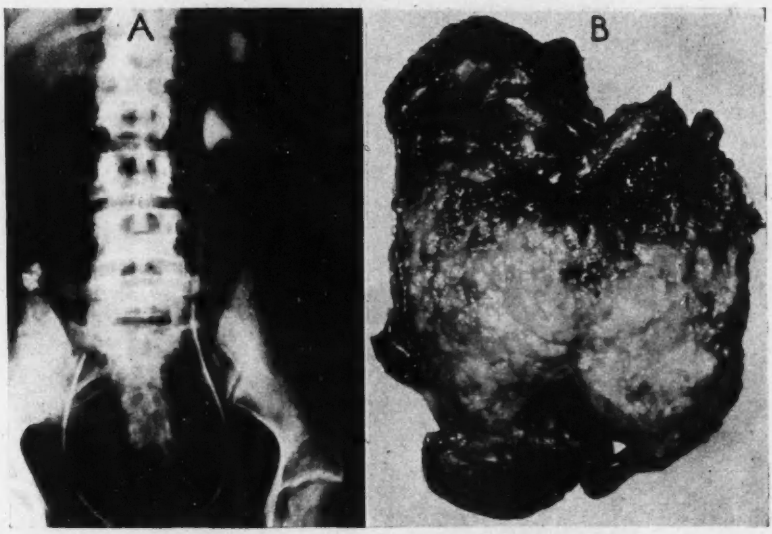

FIG. 1. *A*, Filling defect of left pyelogram. *B*, Cut section of kidney, showing size and relationship of tumor masses.

outer surface of this mass was composed of many lobules of yellow or cream-colored tissue. Interspersed throughout the cut surface were septum-like areas of gelatinous, hemorrhagic tissue. The renal parenchyma was elongated and distorted, and extended over the tumor. The latter lay adjacent but not adherent to the renal pelvis. On opening the renal vein no extension of the tumor was found. On cut surface, the renal cortex was tan, and averaged 1 cm. in thickness. The cortical markings were indistinct, and the glomeruli seemed to be irregularly arranged throughout the cortex. The medulla was pink. Smooth gray mucosa lined the renal pelvis. Stripping of the capsule of the kidney was performed with relative ease, revealing a smooth, mottled surface. The fat immediately surrounding the tumor area appeared quite hemorrhagic and necrotic. The impression from the gross examination was that the tumor resembled a hypernephroma.

A single cross section of the entire tumor was made and several blocks of tissue prepared for microscopic study. These tissues showed a tumor which was com-

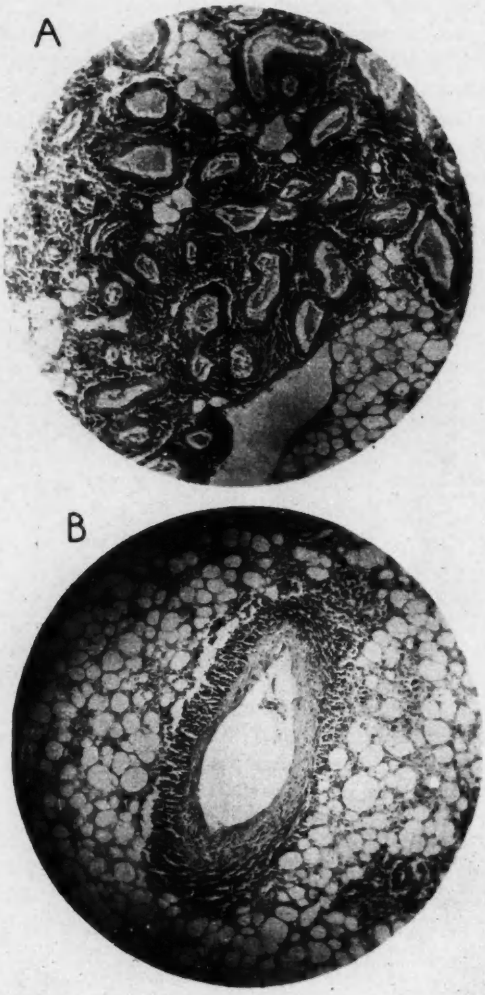

FIG. 2. *A*, Section of tumor. Note vascular components of tumor imbedded in adult fat cells and immature connective tissue. *B*, Higher magnification of one of blood vessels, demonstrating radial arrangement of smooth muscle cells at periphery. Note that vessel is almost completely surrounded by adult fat cells.

posed of several elements (figs. 2 and 3). A part of the tumor consisted of adult fat cells. Another part was composed of large blood vessels that had a peculiar

arrangement of smooth muscle cells radiating from their walls: these smooth muscle cells frequently extended in bundles and groups into fat tissues at a con-

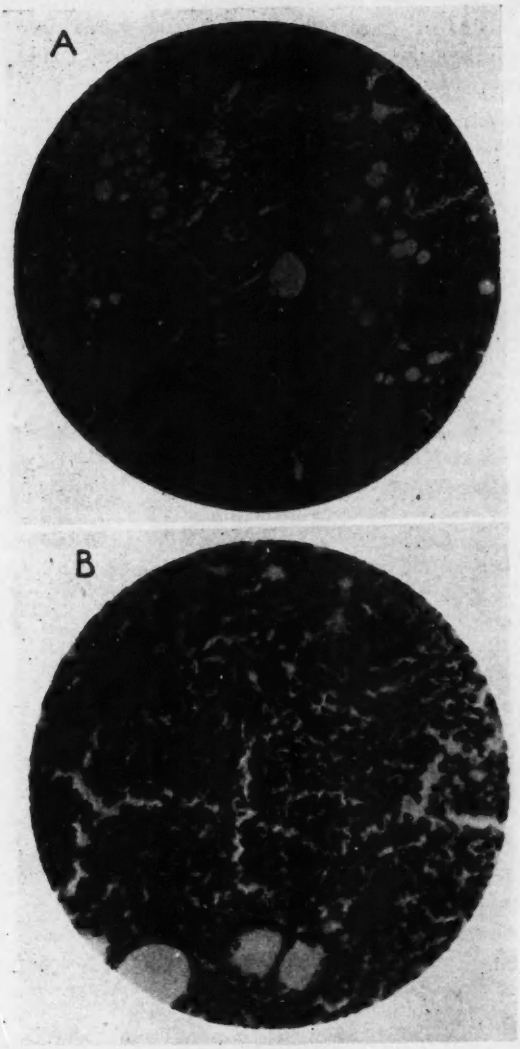

FIG. 3. *A*, Another view of tumor, showing variation in proportion of vascular and stromal components. *B*, High magnification of cellular stroma, showing embryonic character of these cells. Note 3 adult fat cells in field.

siderable distance from blood vessels; as a rule, however, close inspection disclosed a small capillary or artery in the center of each group of smooth muscle

cells. In addition, there were smaller irregular cells that were embryonic in character, resembling immature smooth muscle cells. There were no mitotic figures. The neoplastic cells were not invasive.

These microscopic findings indicated that the tumor was a mixed tumor of the kidney. It should not metastasize, and local recurrence if any should develop very slowly.

COMMENT

Although the tumor presented is predominantly hemangiomatous, the presence of other tissue types leads us to consider it a member of the "mixed tumor" group. Such a classification places it among similar tumors described in the literature under various names dependent upon the dominant histological components. Such terms as "leiomyofibroma," "fibrolipoma," and "adenofibroma" are used to describe individual members of this group which, on morphological grounds, appear to have a common histogenetic basis. The greater degree of differentiation of these tumors segregates them from the allied childhood adenosarcomas of Wilms, and accounts for the slowness of symptoms and the greater life span of these patients.

SUMMARY

A case of a 47 year old woman with a mixed tumor of the kidney is presented.

The term "mixed tumor" includes many tumors of varying tissue types but probably similar histogenesis.

The tumors are slow growing and make their appearance later than the allied but undifferentiated Wilms' tumors.

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BILATERAL EMBRYONAL ADENOMYOSARCOMA OF THE KIDNEY (WILMS TUMOR)[1]

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The occasional true primary bilaterality of embryonal adenomyosarcoma or Wilms tumor of the kidney would seem to confirm the congenital nature of the lesion and corresponds to congenital bilateral tumors in other paired organs—the eyes, ovaries and testes. Doubtless in many cases thought to be primary bilateral Wilms tumor, the growth on one side represents secondary invasion from an initial unilateral lesion. Most reported cases of bilateral Wilms tumor have been found on postmortem examination; rare instances are recorded in the reports of series of renal tumor cases by various authors and to discover these, an enormous mass of literature must be reviewed. Ladd encountered it once in a series of 58 cases. In 17 cases of Kretschmer and Hibbs, one was true bilateral; another showed late secondary invasion of the remaining kidney. Yet in 44 proved cases at the Mayo Clinic, Weisel, Dockerty and Priestley found none bilateral nor did Dean encounter bilaterality in a hundred cases of Wilms tumor at the Memorial Hospital. Children with this condition subjected to bilateral pyelography are indeed rare. In Harrison's patient, a 1 year old male, the diagnosis was made by excretory urography and confirmed at autopsy; each tumor-bearing kidney was approximately 12 cm. long. In 141 cases of Wilms tumor collected from the literature and reported by Walker in 1897, ten were bilateral. Yet it seems likely that in many of these "older" cases, the diagnosis is seriously open to question, it having been made chiefly by palpation; polycystic renal disease or bilateral hydronephrosis may have existed. It is notable that with more widespread urologic investigation in the young the incidence of bilateral Wilms tumor is strikingly less than that indicated in the literature of the turn of the century. A study of the available published case reports since 1930 has revealed those above mentioned and Ueda's case. While there are probably some overlooked and several others not reported or not recognized, the condition is still a rarity.

Herewith are recorded 2 cases of bilateral Wilms tumor. One was subjected to complete urologic examination and the diagnosis was surgically and histologically made; the other was unexpectedly found at autopsy in a 24 day old male. The initial interest focuses on diagnosis (possible confusion with polycystic renal, hydronephrotic or adrenal tumor disease) and secondly on treatment.

CASE REPORTS

Case 1. G. B., 18 months of age, on October 11, 1946 was referred by Dr. Herman Katzman for urologic examination because 1 week previously a large

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

mass had been found in the left side of the abdomen. This mass extended from the costal margin to the level of the iliac crest and nearly to the midline. It was thought that the right kidney was slightly enlarged. The child's previous medical and urological history had been normal. Urinalysis of a catheterized specimen was as follows: yellow, pH 5.5, albumin 1 plus, sugar negative, microscopic examination negative, and culture of the urine was sterile after 48 hours. The blood count showed hemoglobin 8.95 gm. per 100 cc (59.6 per cent); red blood cells 4,070,000 with moderate hypochromia; white cell count 17,700 with 61 per cent polymorphonuclears, 30 per cent lymphocytes, 3 per cent each of eosinophiles, basophiles and monocytes. Roentgenographic examination of the

FIG. 1

FIG. 2

FIG. 1. Case 1. Excretory urogram, showing a large, dense shadow throughout most of left loin. On right, superior renal calyx is compressed medially and elongated. There is slight downward displacement of middle calyx; lower is normal.

FIG. 2. Case 1. Retrograde pyelography more clearly shows finer right pelvic markings and fails to demonstrate any true pelvis on left.

chest was normal except for slight lung compression due to elevation of the diaphragm. Two transfusions of 150 cc each were given with striking benefit.

Just before I saw the boy, an excretory urographic study had been made and showed the shadow of a large mass filling the left loin and no evidence of left renal excretion. On the right the kidney appeared to be slightly enlarged with the lower calyx appearing normal, the middle calyx seemed slightly compressed from above and the superior calyx markedly compressed medially and elongated (fig. 1). Complete urologic examination was then carried out. The left kidney was found to be non-functioning while the right functioned normally as estimated by indigo carmine test intravenously. Bilateral regrograde pyelography showed 2 small round shadows about 1.5 cm. in the region of the left kidney pelvis but no kidney pelvis nor upper ureter as such was delineated (fig. 2). On

the right the retrograde pyelography corresponded in general to that seen in the excretory study but the finer markings were more clearly defined.

A preoperative diagnosis of bilateral polycystic kidney disease was made, the thought being that involvement on the left was universal and the tumor at the superior pole of the right kidney might be a solitary or multilocular cyst since there appeared to be no change in the lower half of the kidney (fig. 1). It was decided to perform left nephrectomy first with subsequent excision of the cyst at the superior pole. In bilateral renal malignancy, treatment offers scant hope yet it seems that even should these renal lesions be found malignant, resection of a kidney showing a relatively small amount of involvement offers an exceedingly long chance which should be taken.

On October 23 the left kidney was explored through a curved loin incision. Palpation of the pedicle did not suggest vascular invasion by the tumor nor were adjacent involved glands found by palpation. The renal surface at once indicated the lesion to be tumor rather than polycystic disease but the surface of the organ seemed much more pale than we are accustomed to observe in Wilms tumor. The kidney was removed with some perirenal fat. A small cigarette drain was left in the perirenal space, the fascia and muscle were closed with double layer chromic suture; the skin and superficial fascia were closed with interrupted dermal sutures. The child's convalescence was stormy but he was returned home on the ninth day.

Pathologic Report (Dr. John L. Work): On immediate gross section of the removed left kidney, the tissue resembled a uterine fibroid or a renal rhabdomyosarcoma. It presented none of the brain-like type of tissue so commonly observed in Wilms tumor.

Microscopic Description: "Sections made immediately for the purpose of preliminary identification of the tumor, fixed in formalin and Helly's fluid and stained with hemotoxalin and eosin show the tumor to have a peculiar, fairly characteristic structure. Scattered here and there throughout the growth are rather well developed, tortuous, tubular and acinar-like structures which are lined by tall cylindrical cells. These have deep staining, finely vesicular nuclei, which are generally situated in the bases of the cells. These tubular structures are surrounded by broad zones of closely packed embryonal cells, the nuclei of which are not essentially different from those of the cells forming the tubules. Both in the epithelium of the tubules and in the undifferentiated cells which surround them, there are frequent mitoses. The islands of undifferentiated cells and the tubules in their centers are in turn separated by bundles of fairly loose spindle cells, thus giving the growth a distinct lobular structure. In the center of some of the dense, cellular islands there are small foci of necrosis. There is no recognizable skeletal muscle, cartilage, or bone in the sections. Diagnosis: Congenital mixed tumor of the kidney (Wilms tumor)."

Gross Description: "The specimen in formalin consists of a large lobulated mass which can be recognized as kidney only by the presence of a ureter. It has been previously bisected. It measures approximately 12 by 12 by 14 cm. over all and weighs 656 gm. The external surface is ragged, and is partially covered by fat. Beneath this there is a tense capsular-like layer in which there are

numerous compressed, but otherwise prominent blood vessels. The original section and subsequent sections show the kidney to be almost completely replaced by an abnormal growth. This forms numerous large lobules which vary from 3 to 7 cm. across. Their cut surfaces bulge markedly, are soft, pale yellow to white, and fleshy. In the centers of some of the large lobules there are retracting, translucent pink areas which are somewhat fibrous in character and from which delicate fibrous tenules radiate. In the centers of some of the lobules there are foci of necrosis and hemorrhage. The tumor appears to have originated in the superior and lateral portions of the kidney and has severely compressed what remains of both superior and inferior poles. The growth has broken into the superior calyx, which it has greatly distended. The lining surface of the calyx is covered by delicate polypoid and papillary tufts, some of which are pale and like the rest of the tumor. Some of these are dark red. The tumor has also broken into the middle calyx, this structure being filled by a large oval mass measuring approximately 6 by 4.5 cm. Where kidney tissue can still be identified, the normal structure is lost and the substance is abnormally pale. The inferior calyx is filled with clotted blood and with tumor which has grown downward from the other two calyces. The pelvis is almost completely plugged with tumor. The portion of ureter removed with the specimen measures 3.5 cm. in length and 0.8 cm. in diameter. It is plugged downward as far as the clamp mark with tumor which has obviously grown downward from the pelvis. The blood vessels have been cut close to the hilum. None of them, however, is grossly plugged with tumor."

Microscopic Description: "The original sections prepared for the preliminary report and additional sections fixed in formalin and Helly's solution and stained with hemotoxalin eosin, Van Gieson stain, and reticulum stain show a growth as described in our preliminary report. In the reticulum stain there is very little reticulum in the islands of embryonic tissue. There are delicate fibers, however, in the connective tissue septa between these. Van Gieson stain shows practically no smooth muscle in the tumor. Multiple sections taken through the hilum and including portions of the walls of the major calyces show tumor to have grown into the mucosa giving rise to large blunt irregular processes on the surface. Some of these are covered by compressed transitional epithelium which is continuous with that lining the calyx beyond the tumor-infiltrated portion. There is obvious compression of the kidney tissue adjacent to the tumor. There is edema in the supporting connective tissue and there is atrophy and disappearance and sometimes fibrosis of the glomeruli and tubules. None of the blood vessels included in the sections are filled with tumor. A longitudinal section taken through the tip of the ureter shows stretching of the wall and compression of the mucosa. There is no actual invasion of tumor into the wall. The growth in the lumen is not attached to the mucosa, and fell out during the section process. Diagnosis: Congenital mixed tumor of the kidney (Wilms tumor), with extension into the calyces, pelvis, and ureter."

After a rest of 3 weeks during which the boy received two transfusions, he was returned to the hospital. The right kidney was explored through a curved loin incision. This disclosed the superior polar involvement to be neoplasm which had

nearly trebled in size since the boy was first seen and now comprised more than three-fourths of the renal mass. Intraperitoneal exploration failed to disclose any tumor-bearing glands and the pedicle was not grossly involved. Having found the right kidney to be malignant, it was replaced and the wound sewed up. The boy was returned home after 8 days where his course has been regressive with increased tumor growth and failing nutrition. Largely at the insistence of his father, roentgenotherapy was intensively but ineffectively given for 4 weeks. Six months postoperative the boy is miraculously still alive though death is imminent.

This case has been reported because of its rarity and because of the diagnostic difficulty in which, on the basis of chance together with the bizarre urographic findings, the lesion was thought most likely to be congenital cystic disease rather than bilateral renal neoplasm. It also emphasizes our therapeutic helplessness. To the writer it seemed that the only hope lay in possible resection of the upper half of the remaining right kidney since the lower half represented the only functioning renal element and, had the disease been cystic rather than neoplastic, the contemplated procedure conceivably might have been successful. Radiation therapy is excluded for obvious reasons; any therapeutically effective dose would have destroyed the remaining secreting parenchyma of the child's only kidney.

Case 2. B. O., a 24 day old white male infant, died of inanition. A postmortem examination was made December 7, 1926 at the New York Nursery and Child's Hospital. The important findings were dextrocardia, transposition of lungs, stomach (small), caecum, colon, spleen and pancreas. Both adrenals were absent. Each kidney was enlarged and showed both grossly and histologically embryonal adenomyosarcoma with associated polycystic disease. There was no record of metastases.

SUMMARY

Two cases of true primary Wilms tumor are presented and their occurrence appears confirmatory of the congenital nature of the lesion. In the first instance, the preoperative diagnosis had been bilateral renal cystic disease but the diagnosis of tumor was confirmed by surgery and histologic examination. In the second case, these conditions coexisted with other grave anomalies and were unexpected postmortem findings.

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DISCUSSION

DR. LINWOOD D. KEYSER (Roanoke, Va.): In connection with the excellent paper of Dr. Campbell, may I present what I believe to be an additional case of bilateral Wilms' tumor. The patient was a female Negro infant, age 17 months, whom I saw in consultation in 1937. The slides show an enormous abdomen, with dilated superficial veins. In spite of the fact that intravenous urography showed only traces of the dye, the child's kidney function was good as measured by the nitrogen retention. However, the infant died after several months, and I was permitted to review the autopsy. The slides show the two kidneys as they were found. The right weighed 8 kg., the left 4 kg.

Sections showed in sequence the polymorphic types of structure which we associate with embryonal adenomyosarcoma of Wilms' type. I believe we can safely say that this is a true bilateral Wilms' tumor. The bones, the lungs, the renal veins and other vascular structures were free of metastases. Dr. Campbell has so well reviewed the clinical and pathologic features of the condition, that additional remarks on my part would be repetitious.

With regard to the paper of Drs. Hamer and Wishard, I should like to show another case of pseudo-bone formation in the kidney. This middle aged woman had a mass in the left kidney, the flat film showing an elongated calcareous streak which on retrograde urography was found to fill a somewhat distorted renal pelvis. The kidney was almost functionless and was removed by nephrectomy. The calcified mass was of bony consistency, attached to the renal pelvic parenchyma, the pelvic wall and extended down through the ureteropelvic junction. It was densely attached to and seemed to grow from the pelvic-ureteral mucosa.

The sections show a cartilagenous type of structure, these elements forming a vertical column of cells undergoing calcification as is seen in forming bone. On staining with the silver nitrate stain of Von Kossa, the section with its calcification nicely demonstrates this pseudo-bone formation. Neither myself nor several pathologists to whom I submitted the sections could demonstrate true osteoblasts with certainty.

DR. JOHN K. ORMOND (Detroit, Mich.): I should like to ask Dr. Taylor if there is any sign of malignancy in those adenomas.

DR. TAYLOR: No.

PRESIDENT O'CROWLEY: Dr. Pearse, do you have anything to say in closing?

DR. PEARSE: I have nothing to add.

PRESIDENT O'CROWLEY: Dr. Taylor?

DR. TAYLOR: Nothing.

PRESIDENT O'CROWLEY: Dr. Hamer?

DR. HAMER: Nothing.

PRESIDENT O'CROWLEY: Dr. Heckel?

DR. HECKEL: Nothing.

PRESIDENT O'CROWLEY: Dr. Campbell?

DR. CAMPBELL: Nothing.

CARCINOMA OF THE PROSTATE: A TWELVE YEAR REVIEW[1]

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During the course of the 12 years from 1932 to 1943 inclusive, the diagnosis of carcinoma of the prostate has been made on 436 patients at the Wisconsin General Hospital. Four hundred cases were used for this study as having carcinoma beyond any reasonable doubt. We have been able to follow 383 cases or 93.7 per cent of the total group.

In undertaking this review we were hoping to find encouragement in the recent methods of treatment. A statistical presentation easily becomes confusing by large numbers of figures. To avoid this contingency as much as possible, discussion of generalities is held to a minimum and our results are presented in a series of charts.

SYMPTOMS

The symptomatology has been repeatedly reported in textbooks and current literature. Our data are presented only as a comparison (table 1). The average age of the patients was 66.1 years; the youngest was 38 and the oldest 93. The average duration of symptoms before admission was 25 months.

The physical findings obviously would depend upon the extent of the disease (table 2). It will be noted that 170 of the cases had metastases at the time of admission.

Table 3 summarizes the methods of treatment used. The 12 years were grouped into 4 year periods to show evident trends. More than one procedure was used on some patients.

Clearly there has been an upward trend in transurethral resections and perineal prostatectomies. The 3 suprapubic prostatectomies were done under the mistaken diagnosis that the cases were benign. Patients with advanced carcinoma prior to 1941, discharged as unfit for surgery, not needing resection or refusing surgery accounts for the large number receiving only supportive treatment (table 4). This group will now completely disappear as they will all have some form of endocrine therapy.

The 1 patient still alive has survived to date 73 months. He has now extensive metastatic lesions causing severe pain in the back and legs. He still refuses treatment. Although the average life span was only 8 months from the time of diagnosis or 33 months from the onset of symptoms, 22 lived much longer. Seven patients survived 9 months, three 12 months, ten 15 months, two 18 months, one 21 months, one 24 months, two 36 months, and one 72 months.

We gained nothing by suprapubic cystostomy (table 5). The average patient lived no longer than the average who received no treatment at all. It is true

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

that the patients in this group had marked obstructive uropathy and advanced renal damage.

TABLE 1

	CASES	PER CENT
Urinary frequency	377	94
Urinary difficulty	290	77
Urinary retention	131	33
Urinary urgency	103	26
Hematuria	97	24
Incontinence	83	21
Pain in extremities and back	132	34
Pain in perineum and bladder	80	20
Weight loss and weakness	108	27
Edema of extremities	21	5

TABLE 2.—*Pertinent physical findings*

	cases
Cardio-vascular	
moderate	153
severe	105
hypertension	62
Tenderness	
abdominal	27
ribs and spine	77
Renal function	
poor	123
fair	245
excellent	32
Prostatic findings on rectal examination	
normal	33
moderately enlarged	198
markedly enlarged	79
indurated	367
local extension	83
Metastasis: Total 170 cases or 42%	
ribs	50
spine	112
pelvis	128
extremities	32
lymph nodes	62
lung	3

X-ray treatment was given to 54 patients, but only 25 received x-ray as the only treatment (table 6).

Note the high percentage of metastatic lesions in this group. The average patient gained 3 months over the one receiving no treatment; however, these patients benefited in that many obtained great relief from pain. In no single instance has x-ray prevented metastasis or stopped its growth.

TABLE 3.—*Methods of treatment*

YEARS	CASES	T.P.R.	PERINEAL	SUPRAPUB. PROSTATEC.	CYSTOS	X-RAY	SUPPORT.	ENDOCR.
1932–35	85	41 48%	1 1.2%	3 3.5%	16 19%	12 14%	20 23.5%	0
1936–39	131	72 55%	5 3.8%	0	12 9.1%	27 20.6%	36 27.4%	0
1940–43	184	121 66%	16 8.7%	0	6 3.2%	15 8%	21 11%	103 56%

TABLE 4.—*Patients receiving supportive treatment only*

Total number of cases 77	
Evident metastasis on admission	51 or 71%
Died in the hospital	14
Not traceable	7
Total number available for study	56 cases
Alive June 1, 1946	1
Died since discharge	55
Average life span from admission to death	8 months

TABLE 5.—*Suprapubic cystostomy only*

Total number of cases 21	
Evident metastasis on admission	9 or 40.9%
Died in hospital following surgery	7
Not traceable	2
Total number available for study	12 cases
Alive June 1, 1946	0
Died since discharge	12
Average survival	8.8 months

TABLE 6.—*X-ray treatment alone*

Total number of cases 25	
Evident metastasis on admission	19 or 76%
Died in the hospital	4
Not traceable	3
Total follow-up cases available	18 cases
Alive June 1, 1946	0
Average survival	11 months

In all 3 cases of suprapubic prostatectomy the diagnosis of carcinoma was made on histological examination of the large glands, removed for benign prostatic hypertrophy (table 7).

Transurethral resection was done on a different type of patient. Only 21 per cent showed metastasis on admission (table 8). They all carried 150 cc of resid-

ual urine as a minimum; their prostates were enlarged, and carcinoma had spread beyond the capsule in many. In some the diagnosis was missed originally and histological examination of the tissue revealed carcinoma.

The 8 patients still alive have lived since surgery 138, 79, 71, 55, 59, 47, 52, and 59 months respectively. Of those who have expired the average survival after initial surgery was 22 months; yet 14 lived 30 months, seven 36 months, four 4 years, five 5 years, three 7 years, and three 9 years. Were it not for the fact that a microscopic diagnosis was made in each instance, one would suspect from the sudden prolongation of life with this method of treatment in comparison to the others that an error had been made. Of this group, 70 per cent were alive at the end of 1 year following surgery. Opponents of this method of treatment

TABLE 7.—*Suprapubic prostatectomies*

Total number of cases 3	
Evident metastasis on admission	0
Died in hospital following surgery	1
Total available for evaluation	2 cases
Still alive	0
Died since discharge	2
Life span 8 and 26 months respectively. The longer survival also had two series of x-ray treatment.	

TABLE 8.—*Transurethral resection alone*

Total number of cases 145	
Evident metastasis on admission	31 or 21%
Died in the hospital	11
Not traced	13
Total available for study	121 cases
Alive June 1, 1946	8
Average survival	70 months
Number of those who have died	113
Average life span from first admission	22 months

may say that it is unscientific and actually stimulates growth of the cancer, the end results indubitably prove that resection has a place in treatment of prostatic carcinoma. The seemingly high operative mortality rate needs explanation. One patient died on the tenth postoperative day from sudden pulmonary hemorrhage due to unsuspected tuberculosis. One died of coronary occlusion on the operating table before 2 gm. could be resected. One death resulted from transfusion reaction; the patient also having a large bladder tumor, transitional cell carcinoma grade 3. Three patients died in 1932 and 1933 from hemorrhage and shock. The remaining 6 causes of death were: Bronchopneumonia 2, uremia 2, pulmonary thrombosis 1, pyonephrosis 1.

Two of these patients who underwent transurethral resection as well as other therapeutic measures arrived in the hospital with a suprapubic tube (table 9). On the others cystostomy was done as an emergency procedure and was later

followed by resection. The average survival in this small group is likewise relatively high.

Perineal prostatectomy was carried out in 22 cases. Six were simple prostatectomies either because the surgeon was not aware of the carcinoma in the large glands or upon exposure found extension beyond the capsule which did not per-

TABLE 9.—*Transurethral resection with other measures*

Total number of cases	12
Evident metastasis on admission	4
X-ray treatment	4
Cystostomy	6
Cystostomy and x-ray	2
Hospital death	1
Total available for study	11 cases
Alive June 1, 1946	2
Survival since diagnosis	70 and 105 months
Died since discharge	9
Average survival after diagnosis	25.2 months

TABLE 10.—*Simple perineal prostatectomy*

Total number of cases	6
Died in the hospital	1
Total followed up	5
Alive June 1, 1946	2
Survival after surgery for an average of 61 months.	76 and 47 months
Died since discharge	3
Survival average	46 months

TABLE 11.—*Radical perineal prostatectomy*

Total number of cases	16
Not traced	1
Total available for study	15
Alive June 1, 1946	8
Average survival since surgery	52.6 months
Died since discharge	7
Average survival	35.8 months

mit the contemplated radical operation (table 10). Needless to say, there was no demonstrable metastasis on admission in any patient.

One of the patients still alive had orchiectomy a year ago for a metastatic lesion. The 3 patients who have died surprise us with survival periods of 36, 78, and 24 months respectively, or an average of 46 months.

There was no operative death in 16 radical perineal operations (table 11). The series is small, and it means that in 400 cases only 4 per cent were considered candidates for radical extirpation, which offers the only chance of cure. Of the 7 patients who died, one committed suicide shortly upon discharge. One died

24 months after surgery of a cerebral accident. Five apparently died from carcinoma. Two of the 5 had orchiectomy and stilbestrol for extensive metastasis (table 12). Eight patients are still alive, but they are not cured. They have survived 64, 66, 56, 50, 47, 45, 31, and 62 months respectively. Three recently have had orchiectomy for metastasis. Three are receiving stilbestrol, 1 mg. daily, showing however neither local recurrence nor metastasis. They may have

TABLE 12.—*Endocrine treatment*

Total number of cases 103	
Also had transurethral resection	72
Perineal prostatectomy	6
Metastases at start of treatment	52 or 50.5%
Stilbestrol	22
Orchiectomy	28
Both	53
Died in the hospital (without surgery)	1
Not traced	3
Total available for study	99
Alive June 1, 1946	43
Well, or minimal complaints	30
Ailing with much complaint	13
Average survival from admission to June	47.4 months
Died since discharge	56
Average survival from admission to death	18.5 months

TABLE 13.—*Endocrine therapy alone*

Total number of cases 23	
Died in hospital	1
Not traced	2
Total available for study	20
Metastasis on admission	16 or 80%
Stilbestrol	5
Orchiectomy	4
Both	14
Alive on June 1, 1946 (lived 52, 46, 45 months so far)	3
Average survival from admission to June	47.3 months
Died since admission	17
Average life span from admission to death	16.6 months

been cured, but only time will tell. These survivors have lived decidely longer since operation (one-half nearly 5 years) than patients treated by any other method mentioned above.

In this entire group many patients died 1 to 2 months following initiation of treatment, arriving here in extremis. Attention is drawn to the fact that all survival periods are given from the time of diagnosis on the original admission. Castration may have been resorted to later upon recognition of the metastatic lesion.

Transurethral resection was carried out in the above group to relieve the urinary obstruction. There was no operative mortality; comparing the above group with those who had only a resection, we find that 86 per cent of those having transurethral operation alone were dead at the end of 36 months, whereas only 46 per cent of those having transurethral operation and endocrine therapy were dead at the end of 40.3 months. The patient's comfort and life expectancy have been appreciably improved.

Although the small group receiving endocrine therapy alone may not be representative, the result of the analysis is significant (table 13). These patients had no obstructive symptoms, but all had advanced carcinoma. Eighty per cent had metastasis when first seen. This is the same type of patient who prior to 1942 was sent home without specific treatment or at best received a series of x-ray treatment. He used to live an average of 8 to 10 months. (See tables 4, 5, and 6.)

DISCUSSION

Comparison of the various methods of treatment is difficult since the indications for treatment were not precisely the same. Thus graphical presentation purporting to show the relative survival would not be a true curve since metastases were present in 80 per cent receiving one type of treatment and only in 25 per cent with another. With any form of treatment there will always emerge out of a group of patients a few who live many years. It seems evident that prostatic carcinoma is extremely slow growing in isolated instances. In this type of gland the method of treatment receives unfair credit. On the other hand, we are dealing with an advanced age group subject to all the degenerative diseases and even without carcinoma, many of them would die of other lesions. But once the diagnosis of carcinoma is made, that is given as the cause of death on the death certificate.

A comparatively large group of patients had no treatment at all or at least only palliation. Nearly all were seen prior to 1940. These patients as a rule had no urinary obstruction; they were poor surgical risks, or they had advanced carcinoma without pain. One had a laminectomy to relieve the pressure on the spinal cord due to a metastatic lesion. Another had a colostomy, the large carcinoma causing complete rectal occlusion. A few refused any form of treatment, and others were discharged with an inlying urethral catheter upon digitalization here. These patients survived an average of 8 months following diagnosis or 33 months from the onset of symptoms. Six of the group lived over 4 years from the onset of symptoms. In the future a like series will be eliminated since the advent of estrogenic therapy.

Suprapubic cystostomy did not prolong the life of the average patient. In addition he has to contend with the apparatus and he certainly is neither comfortable nor happy.

X-ray was never given with the intent to cure. It has, however, improved the pain associated with metastatic lesions in about 50 per cent of the cases for varying lengths of time. This form of treatment will be relegated to a minor role in the future. Estrogens and orchiectomy will be tried first.

Transurethral resection definitely prolonged the average life of the patients. We had 9 per cent survival of 5 years. Five survived 5 years, three 7 years, and three 9 years. These patients are all symptom free. We are under the impression that transurethral resection has a definite place in treatment of carcinoma. It is the treatment of choice in patients with obstruction where the lesion is too advanced for perineal enucleation.

Radical perineal prostatic resection was forever kept in mind when appraising a patient. The following criteria were demanded before the patient was subjected to the operation: 1) The gland had to be freely movable. 2) There could be no evidence of metastasis. 3) The patient had to be a fair surgical risk and have a good life expectancy. The operation probably should not be performed after the seventh decade. Only 16 patients met these requirements. We have not succeeded to effect a 5 year cure in 50 per cent, but 5 of the living have survived 64, 66, 56, 50, and 47 months respectively by June 1, 1946. Three enjoy excellent health. Eight of the 16 are alive and have survived an average of 52.6 months since surgery. How long they will remain alive awaits observing. Nevertheless this operation offers the only chance of cure. A section and biopsy of the suspicious area are always indicated. Should perineal approach be resorted to in all suspicious and questionable cases, more carcinomas undoubtedly would be detected.

The patients who received endocrine treatment do not present a homogeneous nor a closed group. The present group is unselected and has been followed like the others. It has been observed that up to 80 per cent respond to this form of treatment for varying lengths of time, some dramatically within a few days. Immediate results were more frequently noted following orchiectomy, particularly the amelioration of the pain. A few patients admitted on crutches walked out 10 days later symptom free. Estrogen therapy was not a useful supplement in cases of failure with orchiectomy. Side effects of estrogen therapy have been noted in the form of gynecomastia painful nipples, and induction of relative and complete impotence. These symptoms disappeared upon withdrawal of the drug. The observation of the last 5 years clarified for us the indication of type of treatment for the control of androgenic activity. We are using stilbestrol in all cases definitely diagnosed as having carcinoma. Orchiectomy is reserved for those patients who show objective evidence of metastasis.

Estrogenic therapy combined with transurethral resection is the operation of choice for prolongation of life and relief of pain. Early radical perineal prostatectomy is just as safe and offers a hope of cure in about 4 per cent of the patients seen.

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LIPOMA OF THE SCROTUM: CASE REPORT[1]

GEORGE R. LIVERMORE

Lipomata of the scrotum are exceedingly rare. The origin of such tumors is a moot question. I reported a case of lipomyxofibroma of the scrotum in the *British Journal of Urology* in March 1933.

Having recently had a case of lipoma of the scrotum, which had its origin from the spermatic cord, I deemed it of sufficient interest to report it to this Association.

In my report of a lipomyxofibroma, I cited the rarity of such tumors, quoting Stevens, Keyes, Lowsley and Kirwin, Eisendrath and Rolnick, George G. Smith, Young and others, all of whom concurred in the rarity of such tumors. Herman also states they are very rare.

Cecil (1927) reported a case of scrotal lipoma. He quoted Park, who reported a case in 1883 and reviewed the report of 3 other cases. Schiller (1918) reported a case of lipoma of the cord. Cecil says these tumors occur most frequently between the ages of 40 and 60; Lowsley and Kirwin, however, say from 50 to 70. Dubuisky (1916) collected less than 50 cases from the literature. These tumors are often of large size. Brossard's weighed 9 pounds. My case of lipomyxofibroma weighed 3 pounds, 9 ounces, and Bonney (1930) reported a case of fibrolipoma that weighed 20 pounds. The lipoma I am now reporting weighed only 225 gm.

Patel and Chalier collected 37 cases of lipoma of the scrotum from the literature in 1909 and Rubaschow 58 in 1926. Schulte, McDonald and Priestley collected 159 cases of benign neoplasms arising from the spermatic cord in 1939. They do not state the number of lipomata in this series. Quinby (1937) reported 2 cases of lipofibromyxoma and stated that only about 200 cases of neoplasms of the spermatic cord had been reported to that date. He did not state the number that were benign.

ETIOLOGY

Injury may be a factor but the cause, like lipoma in other parts of the body, is unknown. It is often impossible to determine the origin of these tumors. Some say they take their origin from small fatty particles about the cord, break through the tunica and coalesce with the preperitoneal fat. Others say they originate from the testicle and still others from the tunica. In my case when the skin and parietal tunica were incised the tumor resembled an omental hernia.

SYMPTOMS

The only symptoms as a rule are weight and pressure. The mass is semi-solid. It is not painful on palpation; is not translucent and fluctuation is not present unless complicated by hydrocele.

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

DIFFERENTIAL DIAGNOSIS

Lipomata must be differentiated from hernia, hematocele, hydrocele and other tumors of the scrotum. This is often difficult, especially when two or more of the above may be present at the same time.

Aspiration should not be done due to the possibility of hernia or malignancy.

TREATMENT

The tumor should be removed and the operating equipment in readiness for a radical operation should the tumor prove malignant.

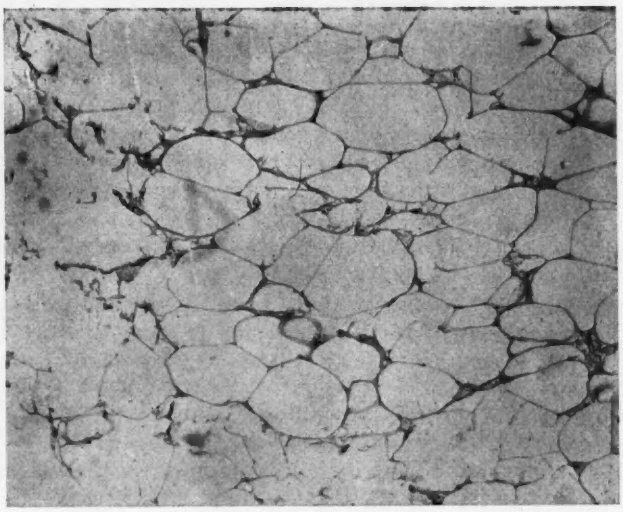

FIG. 1

CASE REPORT

O. M., a white male, married, aged 75, had noticed the left side of his scrotum gradually enlarging for the past year. It was not painful but as it increased in size there was a sense of weight and pressure. He had undergone a prostatic resection by me 6 years ago. The tissue removed at that time showed no evidence of malignancy. The mass was in the left side of the scrotum, semisolid in consistence, and nontranslucent except for a small area about the testicle. The mass was not tender on palpation and the upper limits could be clearly outlined and there was no impulse on coughing and flat on percussion. There was an oval area about 1½ inches long and ¾ inch wide in the centre of the mass about 2 inches about the testicle. It was attached to the cord along with the remainder of the mass. It was firm and tense, and when compressed between the index finger and thumb was tender. This proved to be a lobule of encapsulated fat. The entire mass measured about 6½ inches long and 3½ inches wide. The Aschheim-Zondek and the Wassermann tests were both negative.

My diagnosis was tumor of the testicle, a fibrolipoma, possibly with malignant area. The pathologist was present at operation to give me a frozen section diagnosis. Operation was performed May 10, 1947 and a large lipoma intimately attached to the cord was found. It was easily dissected free from the cord and its attachments to the visceral tunica. The testicle was surrounded by a small section of the parietal tunica and about 15 cc of clear hydrocele fluid was evacuated when the latter was incised. A bottle operation for hydrocele was done. The blood supply of the lipoma was separate and distinct from that of the testicle, consequently there was no necessity to remove the testicle. All small particles of fatty tissue were completely stripped from the cord and the tunica.

The report of the pathologists (Drs. Leake and Golden) was as follows: "The specimen consists of numerous large lobules of yellowish fatty tissue. For the most part, they appear well encapsulated and resemble lipomatous tissue. The entire specimen weighs 225 gm. In one small area there is a hemorrhagic appearing surface and a suggestion of a lining membrane. A section of this area was taken.

"Microscopic examination: Numerous sections of tissue reveal those of large fatty lobules with a small amount of connective tissue stroma and a few blood vessels. Picture entirely consistent with a lipoma (fig. 1). Diagnosis: Lipoma."

Medical Arts Bldg., Memphis, Tenn.

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THE ARREST OF HEMORRHAGE OCCURRING AFTER OPERATION ON THE PROSTATE[1]

DAVID M. DAVIS

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Hemorrhage after prostatic operations is usually spoken of as immediate, on the one hand, and delayed, or late, on the other. Each surgeon employs his own preferred methods for the control of immediate hemorrhage. These methods in general rely on four principles: first, ligature of individual vessels; second, mass ligatures, usually in the form of mattress sutures; third, pressure of packs or hemostatic bags and fourth, electrocoagulation of bleeding points. Ligatures must be of absorbable material, and may therefore give way or be absorbed in a few days. The same is true of the so-called absorbable gauze. Vessels, the bleeding from which is arrested by pressure, may start bleeding again at any time. The burned tissue resulting from electrocoagulation sloughs off after a few days, and bleeding may recommence at that time. For these reasons, there is no way in which late hemorrhage can be absolutely prevented; every urological surgeon must know that it is bound to occur in a certain number of cases, and must be prepared to cope with it in an effective manner and at any time.

In 1915, before this Association, and not in a prepared paper, but in the discussion of a paper by another author, Dr. Frank Hinman stated that he had found a practical way to arrest bleeding after the punch operation. His method was to insert a cystoscope, armed with a flexible electrode, and coagulate each bleeding point separately. Unfortunately this statement did not receive wide publicity. I personally commenced to use this method in 1926. Cary Bumpus began independently to use it about the same time, and published a note concerning it in 1929. The discovery directly after this of the report of Frank Hinman's discussion in the Transactions of this Association effectively eliminated any chance of a priority dispute between Cary Bumpus and myself. With the development of the Stern-Davis and the McCarthy resectors, electrocoagulation became the accepted method of hemostasis after all transurethral prostatic resections.

I should now like to offer evidence that electrocoagulation of individual vessels is the best method for dealing with delayed hemorrhage after any prostatic operation, whether it be suprapubic prostatectomy, perineal prostatectomy, or transurethral resection. Methods previously recommended are the use of hemostatic bags, and of packs. Foley bags may be inserted through the urethra, but Pilcher or Hagner bags require cystotomy if the bladder has not already been opened. In the same way, after perineal prostatectomy insertion of a pack or re-insertion of a hemostatic bag requires reopening of the perineal incision.

Experience has shown that with the panendoscope a bleeding artery can be seen at any point in the prostatic cavity, or around its edges. The sole exception would be when the walls of the prostatic cavity had been drawn together by mat-

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

tress sutures. This however is an academic objection, since as long as the sutures hold, there will probably be no hemorrhage, whereas after they let go, any bleeding vessels can easily be brought into view.

The diagram in figure 1 illustrates how the panendoscope can be inserted after suprapubic prostatectomy or transurethral resection, and, by proper manipulation, expose any portion of the interior of the prostatic capsule.

Figure 2 illustrates how the perineal fistula, if still open, can be used for the insertion of the instrument after perineal prostatectomy. Incidentally, insertion

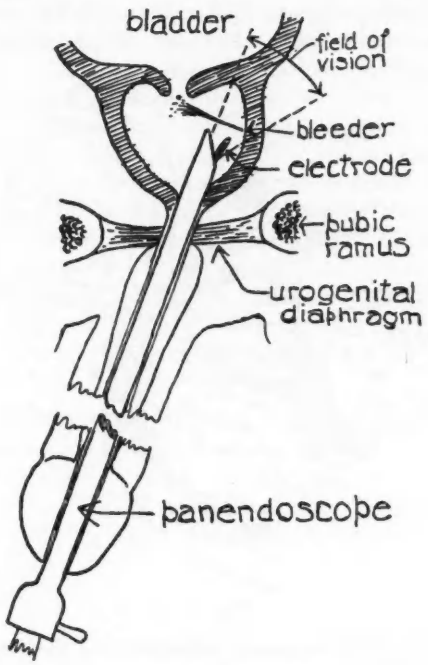

FIG. 1

through a perineal fistula is entirely painless. It also shows how bleeding arteries may be located, even if far up in the sub-trigonal cavity from which a median hypertrophied mass has been removed. It has been found possible to arrest hemorrhage in this manner without even removing the urethral catheter from the bladder. If the catheter has to be removed, it can be reinserted in the bladder, after the hemorrhage is arrested, the panendoscope being used to confirm its position, or if necessary to direct its progress through the vesical orifice.

Troublesome late bleeding is always arterial. Location and coagulation of a single artery are nearly always effective in stopping the bleeding completely and permanently. There are therefore no packs or bags to require attention and subsequent removal. The incision is not disturbed. The postoperative period

is usually not lengthened even by a single day. The finality of the hemostasis is very encouraging to the patient and quickly removes his apprehension. The comparative ease of the procedure brings about its use as soon as bleeding is discovered. This prevents waste of time and the frittering away of the patient's blood and strength due to the use of inadequate and ineffective measures.

Blood clots must of course usually be removed before locating the bleeder. The sheath of the panendoscope is an ideal clot evacuator, and with the assistance of the Toomey syringe and the Ellik evacuator, any quantity of clots can be promptly removed. If any adherent masses of clot resist evacuation, the end of the sheath is thrust into the clot under vision. It is then held steady in this position, the

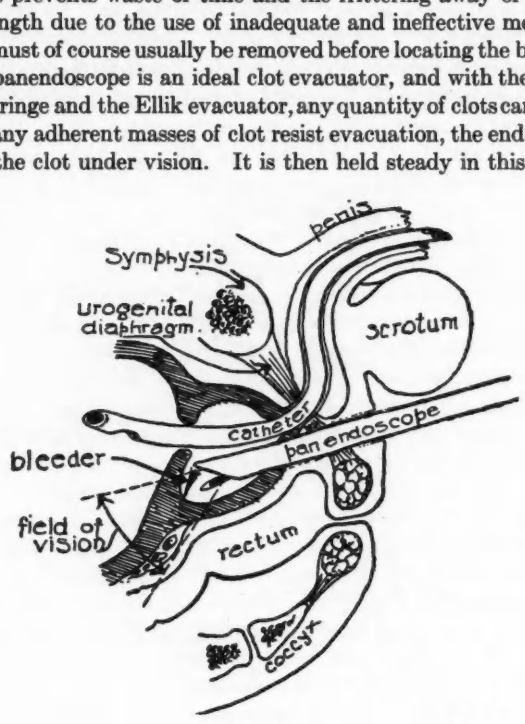

FIG. 2

telescope removed, the Ellik evacuator attached, and the clot patiently rocked back and forth until it disintegrates and comes out through the sheath.

About 7 years ago 3 postoperative hemorrhages occurred in the same patient, 4, 6 and 10 days after suprapubic prostatectomy. On the first occasion, a gauze pack was inserted through the suprapubic fistula. On the second occasion a Pilcher bag was drawn in through the suprapubic fistula. On the third occasion, it was felt that an effort should be made to obtain a more lasting hemostasis. Accordingly a panendoscope was inserted through the urethra under sodium pentothal anesthesia and the bleeding artery found and coagulated. There was no further bleeding, convalescence was quickly completed, and the patient is still in perfect health today. In another case, a very sharp hemorrhage on the fourth day after perineal prostatectomy was arrested in the manner described through the perineal fistula, without any anesthesia and with practically no discomfort to the patient. The catheter was not disturbed. When the catheter was re-

moved on the ninth postoperative day, the perineal incision was entirely healed, and no leakage of urine occurred through it at any time. The patient was discharged as entirely recovered on the twelfth day after operation; that is, 8 days after the hemorrhage.

In a personal series of 486 consecutive cases operated upon by transurethral resection, suprapubic prostatectomy, and perineal prostatectomy, there has been no death from hemorrhage. No bladder has been opened for hemorrhage since 1934 (13 years ago). My confidence in the electrocoagulation method has increased to such an extent that I am inclined to intervene early in every case where there is even a fear that bleeding may be of serious moment. This of course is a radical and fundamental change from the previous guiding principle that one should wait until forced to admit that the bleeding was serious. I am convinced that this change of principle is desirable and in fact greatly needed. When it is followed, one no longer sees any exsanguination whatever after prostatic operations. The method is harmless, so that if one occasionally does intervene in a case which might have survived without it, no damage is done.

Death rates have sunk so low in prostatic surgery that the most meticulous attention to detail is necessary, not only to accomplish a desired further reduction, but actually to maintain and preserve the present good situation. A single unnecessary death may double the mortality rate for a whole year. I offer these suggestions for the control of postoperative hemorrhage as a contribution to this meticulous study of detail in prostatic surgery.

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THE HORMONAL FACTOR IN HETEROLOGOUS GROWTHS OF HUMAN PROSTATIC CANCER[1,2]

CLYDE L. DEMING AND MICHAEL S. HOVENANIAN

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Heterologous growths of human prostatic cancer offer an unparalleled opportunity for controlled study of human prostatic cancer from biological, histological and etiological standpoints. Growth of human cancer outside the body without synthetic carcinogenic agents has been difficult; while the growth of animal cancer in animals has long been successful, and its study has stimulated our efforts to grow human cancer. The chemical carcinogenic agents used to produce cancers in animals are not normally found in man, although the radicals of the carcinogens are being searched for in the glandular organs of man. Specifically, prostatic cancer is exceedingly rare in animals and is common in man. Experimentally induced epithelial tumors of the prostatic gland in animals have undergone metaplasia and developed into squamous cell cancers (Moore and Melchionni; Dunning, Curtiss and Segaloff). In the human, practically all prostatic cancers are of the adenocarcinomatous type. A cancer like the human prostatic cancer, if it were a true biological cancer, should be made to grow in animals, where evaluation of the hormonal factor could be made with greater freedom.

For this purpose we have prepared a series of heterologous growths from a human prostatic cancer of the adenocarcinomatous type which reproduced itself without the influence of any foreign carcinogenic agent through successive generations in male and female guinea pigs. Transplants have been made from one animal to another through ten generations without selection of animals as to strains relative to the susceptibility to cancer. The human prostatic cancer tissue was obtained from a man 69 years of age who had metastases in the lumbar vertebrae and the left vas.

Table 1 shows the number of guinea pigs to which the cancer was transplanted. In all generations 94 males and 28 female animals were inoculated, with 43.6 per cent successful heterologous transplants in the males and 11.3 per cent in the females. Throughout all the generations of transfer the cellular morphology seen in the parent human tumor was maintained. In the first two generations, about 75 per cent of the males grew cancer tissue in the anterior chamber of the eye; while in 3 of the female animals the transplanted tissue remained alive for about 10 days and then disappeared. In the first 5 generations none of the female animals grew transplanted prostatic cancer, which seemed to establish the fact that prostatic cancer requires the male hormone, androgen, for its growth. In the sixth generation 1 female was given 5 mg. of androgen on the day of trans-

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

[2] This work has been supported by a grant from the Connecticut State Cancer Society, Inc., and appreciation for this aid is hereby expressed.

plant and then daily for 35 days. The cancer grew rapidly in this animal. This supplements the former statement and again indicates that when the female hormonal balance was greatly upset in favor of the male hormone prostatic cancer would grow.

In the eighth generation, 50 per cent of both males and females grew tumors. These females were untreated, showing that the tumor had now become feminized and would grow in the female animal without excessive androgen stimulation. Transfers were made into male and female mice which accepted the tissue and produced the cancer growth readily, suggesting that the tumor had become independent of both male and female hormones. In the tenth generation about 40 per cent of males and females grew tumors, emphasizing again that the tumor

TABLE 1.—*Results of heterologous transplantation of human prostatic cancer into the eyes of guinea pigs*

GENERATION	NUMBER OF PIGS		NUMBER OF TAKES		TAKES PER CENT	
	Male	Female	Male	Female	Male	Female
First	7	5	5	2-0*	71.4	0
Second	16	4	12	1-0*	75	0
Third	22	5	8	0	21.5	0
Fourth	10	1	2	0	16.6	0
Fifth	6	0	2	0	33.3	0
Sixth	7	1†	1	1†	14.0	100
Seventh	2	1	2	0	100	0
Eighth	12	2	6	1	50	50
Ninth	4	4‡	0	1§	0	25
Tenth	8	5	3	2	37.5	40
Totals	94	28	41	5	43.6	11.3

* Initially "takes" but within 10–12 days regressed.

† Received 5 mgm. testosterone daily for 35 days starting with day of transfer.

‡ Castrated.

§ Stimulated with testosterone (2 stimulated with testosterone, 1 mg. a day, 1 of which equals take.)

probably was little influenced by male and female hormones. The possibility of its becoming resistant to estrogen seemed plausible in this phase of the experiment.

These experiences with heterologous growths of human prostatic cancer relative to the male and female hormones can be correlated without clinical observations. Nearly 80 per cent of patients with prostatic cancer respond to hormonal therapy, while about 20 per cent of human prostatic cancer cases fail to respond to castration or estrogen therapy. These latter cases are usually patients with well advanced prostatic cancer growths in whom the removal by castration of the androgen factor formed in the testes and even supplementing the upsetting of the balance of sex hormones by added estrogen therapy fail to arrest the cancer growth. Clinically, we have tried to explain these failures by the production of androgen in the suprarenal gland. The behavior of the

heterologous growths with respect to hormonal influences would lead us to believe that in addition to the factor of androgen production by the suprarenal gland prostatic cancer develops a refractory phase to estrogen, thereby emphasizing the independence and autonomy of the tumor. Clinically our greatest disappointment lies in the so-called majority of cases, literally thousands of cases, who respond favorably for varying lengths of time after hormonal treatment and subsequently die of the cancer regardless of castration and the amount of estrogen therapy. We must appreciate that in such cases the cancer has been subjected to a long period of estrogen therapy during which time the cancer becomes resistant to the female hormone. We can not then expect to cure cancer of the prostate by prolonged use of small doses of estrogenic hormone. The behavior of experimental heterologous growths of human prostatic cancer parallels clinical experience and gives evidence in support of this conclusion. There is no doubt that androgen is a factor in the production or the activating agent in prostatic cancer growth. Equally it is true from these experiments that estrogen is an inhibitor of this cancerous growth in that the cancer could not be grown in the female animal until the eighth generation or until the cancer had become tolerant of the estrogen factor.

The acid enzyme factor is lost with the heterologous transplantation of the cancer to the guinea pig. None of the animals with complete filling of the anterior chamber of the eye with the tumor developed any increase in their blood serum acid phosphatase. This observation is corroborated by the failure of the heterologous tumor to take the lead stain for the presence of the enzyme in the fourth and sixth generations. Even though the prostatic tumor has lost its acid enzyme, it appears to grow rapidly and in successive generations more rapidly. The significance of the loss of the enzyme in successive heterologous growths may be that the cancer becomes more and more refractory to the female hormone. A similar condition is found in our clinical experience, for there are some prostatic cancer cases who have little or no elevation of blood serum acid phosphatase and yet show extensive metastatic lesions. These are the cases who respond least favorably to estrogenic hormone therapy and run a continuous downhill course. Woodard emphasizes the fact that when the acid serum phosphatase remains normal in cases with extensive metastatic prostatic cancer there is probably little acid enzyme produced. A persistent normal acid phosphatase in no way assures us that the disease is under control, for she found in 3 patients less acid enzyme in the tissues at death than when the tumor was first assayed, although the patients died of extensive tumor growth. The longer a prostatic cancer grows the more independence of hormonal influence it attains, and it appears both in clinical experience and experimental animal to become refractory to estrogen. See table 2.

If favorable response to the degree of full control of the growth be obtained by hormonal therapy then the androgen factor must be eradicated as much as possible by castration and the administration of large amounts of estrogen. One must assume that there is much variation in the susceptibility of prostatic cancer

to hormonal response, because different patients react differently with equal dosages of estrogen; but the maximum effect could be anticipated if the hormonal treatment was given in the early developmental phase of the cancer growth. There should be, then, no further argument as to when hormonal therapy should be given. To delay hormonal treatment until the patient develops pain from metastases is like locking the barn door after your horse has been stolen. Hormonal treatment should be given as early as possible in inoperable prostatic cases or as soon as a histological diagnosis is obtained. Sporadic cases may be controlled when a "knock out" hormonal influence is applied, but in general we can not expect to cure our cases when we get them late and treat them with homeo-

TABLE 2.—*Phosphatase levels of guinea pigs with and without cancer growing in the anterior chamber of the eye (King-Armstrong units)*

NUMBER	TUMOR-BEARING			CONTROLS	
	Generation	Acid phosphatase	Alkaline phosphatase	Acid phosphatase	Alkaline phosphatase
1				14.1	16.1
2	First	11.8	14.3		
3				8.1	10.5
4				7.3	6.4
5	Second	9.9	8.7		
6				10.9	16.7
7				8.4	13.1
8				1.4	10.6
9	Third	6.1	9.7		
10	Fourth	14.5	16.7		
11				11.1	12.8
12				7.9	10.4
13				12.6	10.6
14				9.4	14.4

pathic doses of estrogen. It is apparent that the same hormonal response is exhibited in these heterologous transplants as is present in the human clinical experience.

CONCLUSIONS

Experience with heterologous growths of human prostatic cancer indicates that androgen is necessary for its growth: a) Prostatic cancer grew only in male animals during the first 5 generations. b) Female animals heavily stimulated with androgen grew prostatic cancer.

Heterologous growths became feminized in the eighth to the tenth generations and grew in female guinea pigs and female mice.

Prostatic cancer became resistant to estrogen.

Prostatic cancer loses its acid phosphatase enzyme in the heterologous transplant but continues to grow rapidly.

This study would indicate that human prostatic cancer in humans and in heterologous transplants responds to the hormones in the same way; and that,

therefore, heterologous growth offers an unusual opportunity for investigative work on human prostatic cancer.

CLINICAL APPLICATION OF HETEROLOGOUS GROWTH OF PROSTATIC CANCER

Prostatic cancer treated with small doses of estrogen becomes tolerant to the hormone, which explains the refractory phase so often seen clinically.

The loss of the acid enzyme factor in heterologous growths and the failure of some of the clinical cases with extensive metastatic cancer to produce an abnormal amount of acid phosphatase are significant in that there is no loss of autonomy of the cancer.

In order to gain the most decisive action of the hormone in the treatment of inoperable cases of cancer of the prostate the hormone should be given: a) Early; b) hormonal bombardment: castration and large doses of estrogen.

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DISCUSSION

DR. WILLIAM P. HERBST, JR. (Washington, D. C.): This prostatic cancer problem is certainly most interesting. I was very much interested to see the work that was done on the guinea pigs, because it seems to me it throws the problem more strongly into the field of the study of the steroid chemistry than any evidence that we have had before. It is a rather interesting problem to determine the dose of our steroids. Dr. Deming has said that we should bombard with large doses. I cannot disagree with that statement with any evidence that I have to present. However, I feel that until we have had the opportunity to compare the clinical course of at least moderate numbers of patients subjected to small doses with another group of cases that have been treated with larger doses, we will not be able to determine whether we shall use small or large doses.

It has been our feeling over a period of time that we have been observing these malignant prostatic patients clinically that we should hold off on all hormone treatment, or the administration of other hormones or pituitary radiation until these conditions exist, namely, that the patient is suffering undue pain due to metastasis, or that he is experiencing a rather rapid, downward trend generally. If it is a matter of obstruction alone, it is our feeling that resection should relieve the obstruction, and we do not advise either castration or the administration of steroids at that stage of the disease. We wait until pain develops, and that is regardless as to the degree of extensiveness of metastasis. In other words, we do not advocate the use of castration or the steroids when we have a demonstrable extensive metastasis.

The reason we feel that way is, it seems to me, at the present time we have had enough experience to observe the fact that the institution of castration, the administration of steroids, pituitary radiation has potentially a certain period of time in each individual. If that is true, and we are interested in the extension of life expectancy, then we should reserve those measures until they are actually needed.

In our observation there has been no doubt about the fact that if we use small doses of the steroids, we will get along particularly with pain relief for a much longer period of time than if we start in bombarding them with large dosages. So that, briefly, our plan of treatment is relief of obstruction by resection, then castration, and then administration of steroids when we lose control by castration, and then subsequently, pituitary radiation, in the meantime supporting the patient with all means at our command.

In closing my remarks, I should say that Dr. Deming has presented a situation where we can investigate the effectiveness of all kinds of chemical substances in so far as their influence on the prostatic carcinoma itself is concerned.

DR. HUGH JUDGE JEWETT (Baltimore, Md.): Dr. Deming is certainly to be congratulated on his beautiful piece of work. There is one question I would like to ask him before this subject is closed. From where I was sitting, it looked as if the original section from the prostate showed typical adenocarcinoma, whereas

it seemed that the section from the transplant showed a rather undifferentiated carcinoma. In fact, in some places it even suggested a poorly differentiated epidermoid carcinoma. If that is true, the metaplasia might possibly explain the loss of acid phosphatase content in the transplant.

DR. J. A. C. COLSTON (Baltimore, Md.): I should like to make a few remarks about Dr. Wear's paper. In the first place, his criteria for the radical operation agree with our own, that the tumor must be freely movable, must not extend beyond the capsule, metastasis must not be present, and especially I think that the patient should have a good life expectancy. Also, his end results, if I understood the figures correctly, were approximately 50 per cent living at 5 years. These agree with our own observations on the results of this operation.

Last year I presented 8 cases in which, on examination, the malignant disease was questionable as far as operability was concerned; that is, there was a possible extension beyond the capsule. We considered that these cases had an unfavorable prognosis for radical operation, but endocrine therapy was instituted. Stilbestrol was given over varying periods of time; in all instances, that is, in the ones that were subjected to operation, the local growth regressed to such a degree that we considered that operation would offer favorable prognosis, and all were subjected to radical operation. In other words, before endocrine therapy, I doubt if any of these cases would have been operated on. From our experience with these cases, we have been tremendously impressed with the advisability of giving preliminary endocrine therapy before radical operation was undertaken. I hope to report later on the progress of these cases. You must bear in mind that they were all unfavorable had they not been subjected to endocrine therapy. One of them has died, and 2 of them have local recurrences at present over a period of about 2 or 3 years.

It seems to me that a certain group of carcinoma cases which would be unfavorable for the radical operation could be transformed into cases that would have a potential curability by preliminary endocrine therapy.

I wanted to ask Dr. Wear if he had made any observations on preliminary endocrine estrogenic therapy in preparing cases for the radical operation. We have been so impressed that even lately in the few cases that one sees which are favorable for radical operation when first seen, we have thought it advisable to give them estrogen on the theory that if a fairly advanced case will regress under estrogen, then an early case would also regress and the chances for an ultimate cure would be enhanced.

I was tremendously interested in Dr. Deming's fascinating work, and I think that the dependence of prostatic carcinoma in his transplants on estrogen has been very clearly demonstrated. I do think that the preliminary administration of estrogen, then, will transform some cases of hitherto inoperable carcinoma into cases which can be successfully carried through a radical operation.

DR. LEON HERMAN (Philadelphia. Pa.): Massive hemorrhage may occur at the time the patient starts to void after suprapubic prostatectomy. Dr. Davis hasn't met with these cases; they will bleed to death unless you stop the hemorrhage rapidly, and sometimes you have to do it in the patient's room. You rip

his wound open, put a bag in as rapidly as you possibly can, and transfuse him, and he is likely to get well.

As regards Dr. Deming's marvelous presentation, it is my impression that heterologous transplants and heterology in the biological sense have not heretofore been successful, certainly not in prostatic carcinoma, and the whole question raises so many problems of interesting and valuable speculation that one must be content with congratulating Dr. Deming on a marvelous and possibly epochal presentation.

Dr. William F. Braasch (Rochester, Minn.): When one reaches my age he is inclined to get to the historical stage. I cannot contribute very much to the store of knowledge on the subject of suprapubic prostatectomy, but I happen to hold in my hand a program of the meeting of the American Association of Genito-Urinary Surgeons of 1927, held at this very place and in this very room, 20 years ago. I notice that among those on the program our friend George Livermore discussed suprapubic prostatectomy. It is evident that he has been at it for 20 years.

In looking over this program, however, it is rather disheartening to note that about two-thirds of the members of the Association at that time are either dead or are no longer in active practice. So you can see what 20 years can do, even to a group of urologists.

I want to make a few remarks concerning the control of hemorrhage following prostatic operations. In 1915, Frank Hagner described a distensible rubber bag to control such hemorrhage. It was widely used. About 10 years prior to this, however, Briggs described a somewhat similar bag, but it received little recognition and was overlooked. Soon after Hagner described his apparatus, Pilcher made some modifications, and the Pilcher bag was used for several years. Further modifications followed, and now the Foley bag is widely employed. It is evident that very often the man who has an original idea or produces an original gadget is lost sight of and the man who has the latest modification is the one who gets the most credit for it.

Dr. John B. Wear (Madison, Wis.): The remarks of Dr. Herbst remind me of 1 case in our group. At the time of his operation 6 years ago he was about 72 years old. He came in with retention, and a diagnosis of carcinoma of the prostate without metastases was made. As he was a physician, he requested that he have not only a resection but also an orchiectomy and stilbestrol. He has lived 6 years and has no demonstrable metastases at the present time. His prostate has regressed somewhat by rectal examination. Recently he returned because of moderate hematuria and a biopsy of his carcinoma was taken. The microscopic sections of his recent biopsy and the slides made 6 years ago are identical. I was expecting to see some change, maybe a few less mitotic figures, but one can't tell one slide from the other.

One case doesn't prove that both orchiectomy and stilbestrol are the treatment of choice, but the slides do suggest that they cause no microscopic changes in the cancer. We are still reserving orchiectomy for those patients who have painful metastases unrelieved by stilbestrol.

I would like to make a remark about hemorrhage. I still think the best way to stop hemorrhage is by tying the bleeding vessel which I do perineally and I have yet to put a bag or pack through the perineum in a perineal prostatectomy.

DR. DAVID M. DAVIS (Philadelphia, Pa.): In regard to the paper of Dr. Wear, and also the discussion of Dr. Colston, I think that Dr. Wear's figure of 4 per cent of cases of carcinoma of the prostate suitable for the radical operation probably comes pretty close to the facts even in the places where most radicals are done. This is entirely too low. Dr. Colston has suggested one method by which the percentage might be raised somewhat, but the most important means by which we are going to be able to raise this percentage is by having more cases diagnosed in the early stages.

I wonder if we should not do as the gynecologists have done, namely, to spend more time and effort attempting to interest, certainly the profession generally, and possibly the general public, in the subject of the early diagnosis of carcinoma of the prostate.

I also should like to call attention again to the suggestion made by Drs. Herbut and Lubin from the Jefferson Hospital at the last meeting of the Mid-Atlantic Section of the American Urological Association, that the Papanicolau stain of smears of prostatic secretion may turn out to be a very useful means of making an early diagnosis of cancer in cases where no definite nodule can be felt. We have already operated upon one or two cases and found cancer was actually present, and have done radical operations.

Secondly, on the work of Dr. Deming, many of the important aspects have already been discussed, but it occurred to me that this is additional evidence to indicate that the indiscriminate use of testosterone in middle aged or elderly men for all sorts of indications, or no indications at all, such as is being now recommended throughout the medical profession, should be condemned. I question whether or not urologists should not individually and perhaps collectively raise their voices against this vicious practice—certainly it seems vicious to me. I wouldn't let anyone give me testosterone.

Certainly in connection with hemorrhage I felt sure that someone at least would arise to indicate that fiddling around with the panendoscope and electrode would be inadequate in case of real bleeding. I assure you gentlemen that this is not true. After all, the biggest bleeding you can get from the region of the prostate is from the inferior vesical artery, and we can stop that very nicely with the panendoscope. It is just a question of practicing at it a little bit.

As concerns bleeding at the time voiding is resumed after radical prostatectomy, I do not understand what is meant by that, because, after all, a radical prostatectomy is the one where bleeding is least likely to occur, since all vessels are ligated individually. Certainly I think if one did a radical prostatectomy and tried to constitute a new vesical orifice, it would be a come-down to have to tear it open and put a bag in. You certainly would get into trouble there.

DR. CLYDE L. DEMING (New Haven, Conn.): I should like to thank you for your interest in this work, and I want you to appreciate that it is the beginning of heterologous human cancer growth which should add much to our knowledge of prostatic cancer.

The body of my paper will contain many points which I have left out, and I have presented to you the salient features.

I wish to thank Dr. Herbst for his discussion.

In answer to Dr. Jewett's question, I would say that all of the heterologous growths show many areas of adenocarcinomatous growth. Whether this tumor will change into the epidermoid type or not, I do not know. There are areas which suggest it, but most areas show an adenocarcinomatous character.

I should like to show a slide, the discussion of which is in the body of my paper, which represents, I think, two or three points which Dr. Herbst brought up. It represents a graph of a patient who had an extensive cancer of the prostate, who had an acid phosphatase of 6 units, and who was given stilbestrol, 10 mg. a day, for 2 weeks. The acid phosphatase fell to normal, 3, in this 2-week period and never rose above that point. The intolerance to stilbestrol is well demonstrated in this man who became nauseated, vomited and developed headaches, and he couldn't take the hormone very long at a time, but during the year he took it off and on. We urged him strongly to take it. We tried various types of estrogen, but it didn't seem to make any difference in his response. After a year, he returned with a tremendous amount of pain, and we did a castration, but his pain persisted. We then placed him on 5 mg. of estrogen. His pain didn't disappear. We placed him on 10 mg. per day, and his pain still persisted, but after we placed him on 15 mg. per day, his pain disappeared.

This slide represents a group of cases which we have under observation that would not tolerate estrogen therapy for some time, but later would tolerate it. It also represents one point which is in discussion, and that is whether or not estrogen is of any value after orchiectomy. This man was not relieved of his pain after orchiectomy but was relieved by addition of large doses of estrogen.

We have 1 patient on 40 mg. per day after orchiectomy failed to relieve him of his pain. At the present time I am in favor of giving large doses of estrogen and giving it early.

DR. NESBIT: What evidence is there that the present relief of pain is due solely to the large doses of stilbestrol that you are giving this particular patient?

DR. DEMING: Orchiectomy didn't relieve it. He has not had any other therapy.

DR. NESBIT: What evidence is there other than coincidence that the present large doses of stilbestrol are the factor which has given him relief from pain? Have you stopped giving him stilbestrol and had a return of pain?

DR. DEMING: I have had other cases where we have diminished the stilbestrol and the pain came back again. Fifteen milligrams of estrogen will relieve them. Diminish the dosage down to 10 mg., and the pain will return. This experience has been repeated several times, so the reaction must definitely be due to estrogen therapy.

DR. HERMAN: Are those same months represented by orchiectomy, no pain, the months on the left?

DR. DEMING: Those are 2-week intervals.

ROLE OF THE EXTERNAL URETHRAL SPHINCTER IN THE NORMAL BLADDER AND CORD BLADDER

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Considerable progress has been made in the past few years in the treatment and care of cord bladders resulting from traumatic, inflammatory, neoplastic and degenerative lesions of the spinal cord. It has been satisfactorily demonstrated, we believe, that with suitable care (which includes transurethral resection of the vesical neck in many cases), in the majority of cases, urosepsis can be eliminated and satisfactory vesical function can be established. By the term "satisfactory vesical function" we mean that incontinence is eliminated so that the patient can be kept dry, the bladder is able to empty its contents completely, leaving no residual urine, and the patient can either initiate micturition at will or has sufficient warning of impending micturition so that he has time to procure a urinal. It also stipulates that the capacity of the bladder is sufficient to allow the patient from one and a half to several hours between evacuations of urine.

The care of the cord bladder immediately after the onset of a lesion of the spinal cord has been considered by Prather. He has stated that a closed system of irrigation (either manual or tidal), consisting either of a suprapubic tube or urethral catheter, is the treatment of choice.

The treatment of the chronic phase of neurogenic vesical dysfunction is a more involved problem. It is our opinion that transurethral resection will be necessary in a considerable proportion of cases. In some cases it may not be required until 2 or 3 years after the onset of the lesion of the cord. Opinion differs as to the percentage of cases in which resection will be required. In Prather's series of cases (war injuries) only one transurethral resection was done in a series of 61 cases. In a similar group of cases of war injuries to the cord, Bumpus, Nourse and Thompson found it necessary to perform transurethral resection in 58 of 101 cases.

We have stated in previous articles that we believe most true cord bladders eventually become hypertonic and trabeculated to some degree. This process seems eventually to involve the vesical neck (internal sphincter), which is simply the edge of the detrusor muscle. The spasticity and hypertrophy of the vesical neck or its inability to relax (or both) apparently acts as an obstruction at the vesical outlet and is responsible for the residual urine and vesical disability. Even though this may not be apparent within the first few months or year or

so after the onset of the lesion of the spinal cord, it is nearly always apparent in cases in which the lesion has been present for a long time.

We have had a most encouraging experience with transurethral resection in cases of cord bladder. If we were to stipulate any one condition which should be present in order to insure a good result from transurethral resection, it would be the presence of a substantial amount of residual urine. Fortunately, residual urine is present in most cases. We have had considerable difficulty in distinguishing an automatic bladder from an autonomous or "nonautomatic" bladder. This is not difficult in cases in which the bladder evacuates urine at fairly regular intervals of an hour or more but in cases in which evacuation occurs more frequently and irregularly an automatic bladder is difficult to distinguish from the type of bladder which we have regarded as autonomous or "nonautomatic." In cases of the latter type of bladder, there are frequent spurts of urine which have been regarded as "overflow" or the result of arrhythmical inefficient contractions; these apparently are initiated in the detrusor muscle entirely independent of the central nervous system. We have also found it difficult to correlate the type of vesical dysfunction with the site, severity, or completeness of the lesion in the spinal cord. Our experience in this field, however, has left us with the impression that a satisfactory result is more easily achieved with transurethral resection in cases of autonomous (nonautomatic) bladder than it is in cases in which the bladder is of the automatic type. This is especially true if the lesion is sufficiently low that the abdominal muscles are still intact or partially so, in order that the patient may employ intra-abdominal tension to assist in micturition. This statement is apparently at variance with that of Munro, who expressed the opinion that in cases in which the bladder is of the autonomous type it is most difficult, if not impossible, to secure satisfactory vesical function without resorting to the use of an urethral catheter.

In considering this subject, one is likely to overlook some of the pertinent and accurate observations that have been made in the past. After World War I, numerous studies were made on this problem by many competent observers. One of the best of these is that of Head and Riddoch. Among the conclusions they drew from their study one might mention the following: 1) The site of the lesion can not be correlated with the type of vesical dysfunction. 2) It is difficult to distinguish an automatic bladder from an autonomous bladder. 3) A true automatic bladder can result even if the cauda equina or the lower portion of the cord is destroyed and the bladder is separated from all connection with the spinal cord. 4) Mass reflexes and flexor spasms of the lower extremities and abdominal muscles tend to cause more frequent evacuation of the bladder at lower degrees of vesical filling. This results in a troublesome type of automatism and frequent irregular evacuations of urine. 5) In cases of a complete lesion of the cauda equina or lower portion of the spinal cord in which the bladder is completely separated from the cord, these mass reflexes would not incite vesical contractions and decrease vesical capacity. 6) Most automatic bladders do not empty their contents completely. 7) In cases of automatic bladder, evacuation of urine is

governed by three factors: a) response to tension of the vesical wall, b) relaxation of the tonic (internal) sphincter (vesical neck) and c) the effect of intravesical reflexes. 8) The development of an automatic bladder is dependent on the ability of the internal sphincter (vesical neck) to relax. 9) In some cases in which automatism has not appeared spontaneously, if an urethral catheter is inserted to abrogate the action of the sphincter mechanism, an automatic bladder will result (voiding through the catheter).

It is interesting to note that Head and Riddoch recognized that the most common situation encountered is a hypertonic bladder which is unable to evacuate its contents completely because of an excessively tonic sphincteric mechanism which apparently is unable to relax. This we consider to be the great underlying principle in the problem of the cord bladder; it is the reason why transurethral resection of the vesical neck is successful in a large proportion of cases. This thesis we have explained in previous communications. Recent experience has, we believe, demonstrated that not only is the vesical neck (internal sphincter) a factor, but in some cases abnormal degrees of flaccidity or spasticity of the external urethral sphincter or inability of the external sphincter muscle to relax are factors of importance which must be corrected to achieve satisfactory vesical function in the neurogenic bladder. The remainder of this paper will present our views and experiences on this subject.

As we have stated previously, we feel that a great deal has already been accomplished in the treatment of cord bladder. It is our opinion that in the majority of cases the patients can be treated successfully with proper immediate care and subsequent transurethral resection of the vesical neck when necessary. It should not be intimated, however, that the problem has been completely solved by any means. Each patient with a cord bladder still presents an individual problem that may require all of the ingenuity the physician may possess. There are still several basic problems which require solution. Among these problems, the following may be mentioned: 1) The therapeutic problem of the cord bladder which contains little, if any, residual urine (this type of bladder is frequently seen in children with myelodysplasia caused by spina bifida occulta); 2) the problem presented by the small group of patients with cord bladder who are unable to empty the bladder despite repeated transurethral resections of the vesical neck; 3) the problem of the irritable automatic bladder which can be made to empty completely by transurethral resection of the vesical neck but in which the intervals between evacuation of urine are too short and irregular. This type of vesical dysfunction is often aggravated by extravesical reflexes from spastic lower extremities.

PROBLEMS 1 AND 2

For some time our attention has been directed to the external urethral sphincter as a contributing factor to problems 1 and 2. For instance, in cases in which the cord bladder contains very little urine and passive leakage of urine occurs almost continuously or active incontinence occurs frequently (problem 1), we have wondered if the external sphincter may be at fault. Cystoscopically, the appear-

ance of the bladder (trabeculated) and of the vesical neck (usually hypertonic) is much the same as it is in any case of cord bladder in which urinary retention is present. Is there an absence of normal tonicity or flaccid paralysis of the external urethral sphincter such as is observed in skeletal muscle elsewhere in the presence of a lesion of the lower motor neuron?

In a case of cord bladder in which it is impossible for the patient to micturate or to empty the bladder completely after repeated transurethral resection of the vesical neck (problem 2), what is the nature of the impediment that holds the urine back? The only obvious obstruction left would seem to be the external urethral sphincter. Does it become hypertonic, spastic and hypertrophic and cause urinary obstruction? If the external sphincter is a factor in either of these conditions mentioned, then what is the function of this sphincter in the normal person? What is its normal state—one of neutrality, flaccidity or tonicity? Two cases in which the patients recently were treated successfully at the Mayo Clinic seem to throw considerable light on problem 1. One of these cases will be reported very briefly.

Case 1. A girl, aged 17 years, came to the clinic in September 1945. She had been well until 1940, at which time an operation had been performed for spina bifida cystica. The patient had had no disability from this condition, but operation had been advised to avoid future trouble. After the operation, urinary retention developed and was followed later by vesical and rectal incontinence. Areas of complete anesthesia had developed in the saddle area and on the posterior aspect of the right thigh, and complete anesthesia had occurred below the right knee. This had resulted in a decubitus ulcer of the right heel, which had exposed the os calcis and had produced extensive osteomyelitis. An extensive decubitus ulcer had developed on the right buttock and had exposed the ischial tuberosity.

From the urologic standpoint, the patient was continually wet. Small spurts of urine would issue from the urethra every 3 to 8 minutes. On several occasions, less than 30 cc of residual urine was found in the bladder although on one occasion 60 cc was obtained. Cystoscopy revealed that the bladder was moderately trabeculated and of large capacity. Because of the small amount of residual urine, it was believed that transurethral resection of the vesical neck would be of little help. We wondered, however, if the tone of the external sphincter could be improved with a muscle plicating type of operation, such as the Kelly operation, on the urethra. It was decided to try both procedures.

On October 22, 1945, transurethral resection was performed, and a total of 3 gm. of tissue was removed from the entire circumference of the vesical neck. After the operation the vesical function was not changed except that the small amount of residual urine had been eliminated. The urine still was expelled from the bladder in small spurts every 3 to 8 minutes. A Kelly operation on the urethra was then performed. After removal of the catheter, the patient was able to void every 2 hours and remained dry. If awakened once at night to void, she did not wet the bed. She was able to empty the bladder completely. Sixteen months have elapsed since the operation was performed. The vesical function is still normal and the urine clear. She can initiate micturition at will.

After the urologic treatment the patient's right leg was amputated below the knee and a decubitus ulcer of the right buttock was excised. Both wounds healed well and have remained healed. The patient walks well on her artificial limb and, despite the fact that the stump is anesthetic, she has as yet had no trouble with trophic ulcers.

Case 2. Not long after case 1 was observed, another young girl of about the same age came to the clinic because of the same type of vesical dysfunction. Her trouble had been present since birth and was due to a spina bifida occulta which had never been operated on. The same treatment was employed as in the first case, except that the Kelly operation on the urethra was done first. The procedures were reversed in this case because, although the bladder was extremely trabeculated, the urethra was not more than 1 cm. in length. After the Kelly operation was performed, the urethra was of normal length and an abnormal amount of tissue was present at the vesical neck. This operation was complicated by delayed postoperative bleeding which is fairly common after transurethral resection on women. This necessitated repeated cystoscopy for hemostasis and resulted in a severe urinary infection which required treatment for some time.

After the successful treatment of the patients in cases 1 and 2, an attempt was made to use the same operative procedure on girls who were less than 10 years of age. It was found that the vagina was too small to permit the satisfactory performance of a Kelly operation on the urethra.

At about the same time these cases were being studied we encountered a case which illustrated problem 2. The patient was a young man who had a traumatic lesion of the cord at the level of the twelfth thoracic vertebra. After multiple resections of the vesical neck, complete urinary retention persisted. The patient was finally relieved when suitable treatment was directed toward the external urethral sphincter, which apparently was spastic and causing obstruction.

Case 3. A man aged 30 years came to the clinic in January 1946. He had been injured in an automobile accident almost 2 years previously. There had been a fracture of the twelfth thoracic vertebra and immediate paralysis of the lower extremities, bladder and bowels. Catheter drainage had caused a periurethral abscess. The abscess had been incised at the penoscrotal junction and an urinary fistula had resulted. Vesical calculi had developed. A suprapubic cystostomy had been performed but the opening in the bladder had been allowed to close. An urethral catheter had again been used for drainage.

When the patient came to the clinic he had the typical appearance of a paraplegic. The level of the lesion was found to be at the first lumbar vertebra. There was complete paralysis of the lower extremities aside from slight weak residual motion in the left quadriceps and adductor muscles. The abdominal muscles were normal. There was complete anesthesia of the saddle and perineal areas and over most of both legs.

Urologic examination disclosed a staghorn calculus which filled the pelvis and calyces of the right kidney. There was complete urinary retention. When the bladder contained from 800 to 1,000 cc of urine the patient would complain of severe distress, but would be unable to pass any urine. The old urethral fistulous

tract at the penoscrotal junction could be palpated but did not seem to be patent. Cystoscopy revealed a typical trabeculated hypertonic bladder with some deformity of the left wall and spasticity and contracture of the vesical neck.

In addition to the paralysis and the urinary difficulty, the patient complained of pain in the region of the gluteal muscles on the left, of some pain in the left leg and in the right leg and of occasional twinges of pain in the right renal area. It was observed that filling of the bladder or pinching the skin in the anesthetic perineal area would produce painful reflex spasm of the gluteal muscles on the left side.

Transurethral resection of the vesical neck was performed and 6 gm. of tissue was removed from the entire circumference of the vesical neck and prostatic urethra. After this procedure, the patient was still unable to micturate. The bladder would become distended and provoke recurring episodes of bleeding. Finally, a suprapubic tube was placed in his bladder and he was allowed to go home for a few months.

When he returned to the clinic, transurethral resection was performed on two more occasions and less than 3 gm. of tissue was removed at each operation. There was no more tissue that could possibly be removed. The result was essentially the same as it had been previously and the patient was still unable to void. Vesical spasm again caused repeated episodes of postoperative hemorrhage.

Attention was then directed to the external urethral sphincter. We reasoned that with the vesical neck completely resected and apparently no longer capable of being an etiologic factor, there must be some other obstruction in the urethra to account for the fact that the patient could not force urine out of the bladder with his powerful abdominal muscles. The external sphincter seemed to be the only other possible source of obstruction. In order to relax it, we produced a transsacral block with procaine hydrochloride. As soon as the anesthetic took effect, the patient could void easily with a good stream and could empty his bladder completely. As soon as the anesthesia wore off, however, the patient was again unable to void.

We then thought that the probable factor which had allowed the patient to void was the blocking of the nerve supply of the external urethral sphincter, which possibly allowed the sphincteric muscle to relax. In an attempt to prove this, we again produced a transsacral block with procaine hydrochloride but made cystourethrographic studies before and during the anesthesia. We were surprised to find that the external sphincter was extremely spastic (fig. 1, *a*) before the transsacral block was produced. During the sacral block, however, there was marked relaxation of the sphincter (fig. 1, *b*). This information seemed to lend weight to our belief that the external sphincter was the cause of the obstruction.

There was another factor, however, which had to be eliminated before this opinion could be proved. The transsacral block should also anesthetize the pelvic nerves (nervi erigentes) which arise from the second, third and fourth sacral nerves. We could not be sure that this was not a factor in permitting the patient to void. To eliminate this possibility, we blocked the pudendal nerves with procaine hydrochloride in the area in the perineum where they emerge from Alcock's canal. Again, cysto-urethrograms were made before and during the

anesthesia. The results were the same as those produced by transsacral block, that is, the patient was able to void and empty the bladder and the urethrogram (fig. 1, *c*) again showed that the spastic external sphincter was relaxed during the anesthesia. Spinal anesthesia then was produced with procaine hydrochloride

FIG. 1. *a*, Cysto-urethrogram showing spasticity of external urethral sphincter in case 3; *b*, relaxation of external urethral sphincter during sacral block; *c*, relaxation of external urethral sphincter during bilateral pudendal block with procaine hydrochloride; *d*, relaxation of external urethral sphincter after section of anterior and posterior roots of fourth and fifth lumbar and five sacral nerves.

and the results were essentially the same as they had been previously except that they were not so good as those produced with transsacral block or pudendal block.

It seemed quite clear from these studies that section of the pudendal nerves or rhizotomy of the sacral roots would relax the external sphincter and allow the patient to void. Accordingly, section of the pudendal nerves was advised. The right nerve was sectioned first and the left nerve was sectioned a few days later. The operation was done in the perineum where the nerves emerge from Alcock's

canal. Much to our surprise, this did not yield the same results as did the injection of procaine hydrochloride; therefore, we felt that some fibers had not been sectioned. It was then decided to perform an anterior rhizotomy of the sacral roots. Laminectomy was performed and the cauda equina was exposed. The roots of the sacral and coccygeal nerves (which were lying mesial to the roots of the lumbar nerves) were separated from the roots of the lumbar nerves. The anterior roots of the sacrococcygeal nerves were then separated from the posterior roots and divided between silver clips; about 0.5 cm. of the roots was removed on each side. This did not produce the desired results. The urinary retention persisted and the pain and gluteal spasm continued and caused the patient to become addicted to demerol. It was then decided to perform a complete section of the roots of the sacral nerves and possibly the roots of the last two lumbar nerves to be sure of denervating the external urethral sphincter and gluteal muscles. The lower portion of the thoracic segment of the spinal cord and the entire conus medullaris were exposed. Because of dense adhesions from the previous operation, it was impossible to separate the fibers of the cauda equina sufficiently to identify what had been severed previously. In order to sever completely all of the sacral nerves and the roots of the fourth and fifth lumbar nerves, three ligatures were passed around the entire cauda equina at the level of the third lumbar vertebra. All the anterior and posterior roots were divided below this ligature so that the roots of fourth and fifth lumbar and the roots of the first, second, third, fourth and fifth sacral nerves were completely severed.

The result of this last procedure was excellent. The pain and gluteal spasm disappeared and the patient was able to void voluntarily with a good stream. An urethrogram (fig. 1, *d*) showed that the external sphincter was relaxed. The patient was able to void 10 to 12 ounces of urine with a large continuous stream by using abdominal straining. At first, 150 cc of residual urine persisted but after 10 to 12 days the patient was able to empty his bladder completely. The patient was able to retain his urine and to keep dry. The only time he lost any urine was when the bladder contained more than 400 cc. If he then strained considerably (as for instance when performing his exercises in physical therapy), a few drops of urine occasionally were expelled. This could easily by controlled by not allowing the bladder to become too distended with urine or by using a penile clamp for a short time with very little compression.

Before he was ready to be dismissed, it was decided to remove the stone from the pelvis of the right kidney as it was beginning to cause pain. A right pyelolithotomy was performed. During his convalescence from this procedure, a periurethral abscess developed at the site of the original abscess and the old fistula opened and drained at the penoscrotal junction. This complicated the situation somewhat as urine ran out of the fistula when he voided. It, therefore, was difficult for him to keep dry. We advised him to return in a few months for closure of the fistula if it did not close spontaneously.

The patient returned 3½ months later for re-examination. The fistula had closed spontaneously and the patient was apparently voiding well. Examination, however, disclosed the presence of 200 cc of residual urine. Cystoscopy

revealed that a postoperative band of scar tissue had formed across the posterior lip of the vesical neck. This was excised with the resectoscope by removing four small pieces of tissue. This allowed the patient to empty his bladder completely. He was allowed to return home.

He returned for re-examination 3 months later. Examination disclosed that the bladder contained less than 60 cc of residual urine. The patient was able to void a normal urinary stream by using abdominal pressure. If the bladder was allowed to become distended with more than 250 or 300 cc of urine, the patient might lose a small amount of urine if he strained too hard with physical exercise such as getting himself in and out of bed; otherwise, he remained dry.

The evaluation of this case is not simple. It would seem logical to assume that the obstructive factor in this case was the external urethral sphincter. On the other hand, it is not entirely clear if the hypertonicity (or the inability of the sphincter to relax) was a typical response of skeletal muscle to a lesion of the upper motor neuron or the result of stimulation from extravesical reflexes from the lower extremities and spastic gluteal muscles. It could have been from a combination of these factors. One also wonders why complete passive incontinence does not occur in a cord bladder after a combination of transurethral resection of the vesical neck and destruction of the nerve supply of the external urethral sphincter (by rhizotomy). It would seem that there must be enough urethral resistance or passive (neutral) tonicity of the external urethral sphincter to prevent incontinence of urine. In cases of autonomous bladder in which transurethral resection has produced good results, the patients can initiate micturition at will if there is a substantial amount of urine in the bladder. This is done by increasing intra-abdominal tension by setting the diaphragm and contracting the abdominal muscles (if they are intact). The patients may lose a few drops of urine if they allow the bladder to become too full and then engage in some strenuous type of exercise. In other words, the problem is the same as urinary retention in a patient who does not have a neurologic lesion, that is, one of vesical force versus the sphincters (vesical neck and external sphincter).

CYSTO-URETHROGRAPHIC AND CLINICAL STUDY OF THE EXTERNAL SPHINCTER

In order to obtain more information about the function of the external urethral sphincter, we made a cysto-urethrographic study of 5 persons who did not have any neurologic lesion and of 10 patients who had lesions of the spinal cord and associated vesical dysfunction.

The technique which we employed is simple; it is essentially the same as that described by Flocks and Alcock. Approximately 30 cc of sterile K-Y lubricating jelly is mixed with 20 cc of some type of radiopaque oil. This medium should be mixed just before it is to be used.

The injection of the medium is made with a 50 cc syringe that is attached to a piece of rubber catheter about 3 inches (7.62 cm.) long. The patient is placed on his back on the x-ray table. One of the patient's hips is then elevated to an angle of approximately 15° and held there with a small wooden block. This position is employed to throw the shadow of the urethra away from the pelvic bones. The

penis is then firmly grasped in the left hand, the short piece of urethral catheter (attached to the syringe) is introduced into the urethra and about 25 cc of the medium is injected slowly with firm pressure into the prostatic urethra and

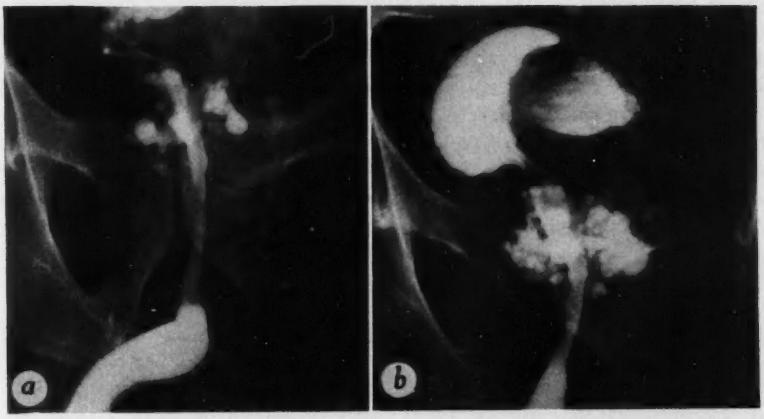

FIG. 2 Cysto-urethrogram of man who did not have a neurologic lesion; external urethra sphincter apparently in "neutral" position; *a*, before pudendal block; *b*, during pudenda block with procaine hydrochloride.

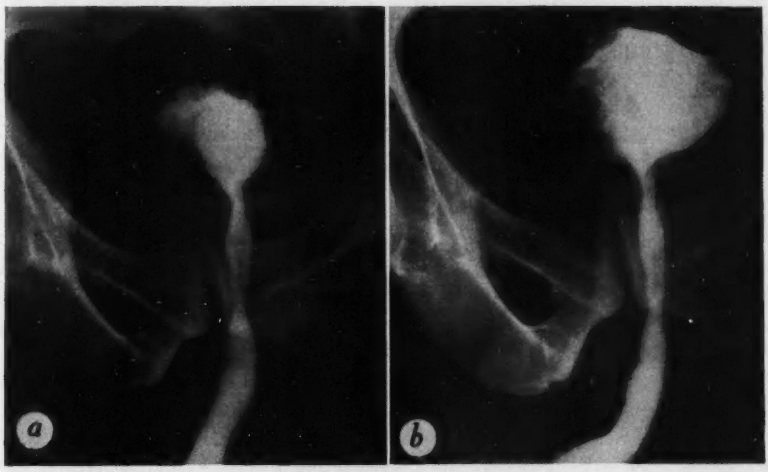

FIG. 3. Cysto-urethrogram of man with no neurologic lesion but who had an extensive tumor of bladder; external urethral sphincter apparently in "neutral" position; *a*, before transsacral block; *b*, during transsacral block.

bladder. As the medium is being injected the first film is exposed (by using a Bucky diaphragm). A second film is exposed while the medium still is being injected.

Study of persons who did not have any neurologic lesion. After preliminary cysto-urethrograms had been made, the pudendal nerves were blocked or trans-

sacral block or spinal anesthesia was produced. Procaine hydrochloride was the anesthetic agent used in each instance. The bladder then was filled with fluid and in studies in which transsacral block and pudendal block were employed the subjects were helped to their feet and observed for evidence of incontinence of urine. They then were asked to micturate. In the presence of bilateral pudendal block, all of the subjects were able to void normally; micturition could be initiated at will and there was no leakage of urine when the subjects were in various positions. In the presence of sacral block or spinal anesthesia, there was no leakage of urine (during spinal anesthesia, the subjects were not made to stand on their feet) but the subjects were unable to initiate micturition.

Another cysto-urethrogram was made while anesthesia still was present. In each instance, the preliminary cysto-urethrogram disclosed that the urethral

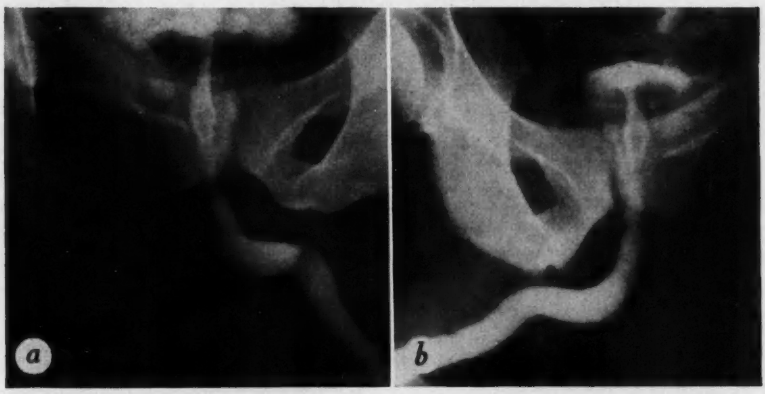

FIG. 4. Cysto-urethrogram of man with no neurologic lesion who had extensive hypertrophy of prostate gland; external urethral sphincter apparently in "neutral" position; *a*, before sacral block; *b*, during sacral block.

sphincter was in a more or less "neutral" position. The cysto-urethrograms that were made while anesthesia was present did not reveal any change in the appearance of the urethral sphincter (figs. 2, 3 and 4).

Studies of patients who had lesions of the spinal cord. In 7 of the 10 cases in which lesions of the spinal cord were associated with neurogenic vesical dysfunction, the preliminary cysto-urethrogram showed evidence of increased tonicity of the external urethral sphincter (fig. 1, *a*). In 3 cases, there was either no evidence of increased tonicity or definite evidence of relaxation or flaccidity (fig. 5). Further analysis of these cases is most interesting.

In all of the 7 cases in which the cysto-urethrogram disclosed increased tonicity of the external urethral sphincter, there was evidence of varying degrees of reflex spasticity and contraction of the muscles innervated by segments of the cord below the level of the lesion (principally of the lower extremities). In 2 of these cases, the lesions were incomplete, they had been present for a long time; the patient had recovered sufficiently to walk with crutches, but deformities of the

lower extremities persisted owing to spastic contractures. The duration of the lesion was more than 2 years in all of these cases except one, in which it was 8 months. It is interesting that this was the only case in which trabeculation of the bladder was not present. In 6 of the 7 cases the lesion was situated between the fifth thoracic and the third lumbar vertebrae; in the remaining case, it was situated at the level of the fifth cervical vertebra. Four of the patients were studied with either one or more of the following types of anesthesia: bilateral pudendal block, transsacral block and spinal anesthesia. In all of the 4 cases, cysto-urethrograms made while the anesthesia was in effect showed relaxation of the spastic external urethral sphincter (fig. 6). Transurethral resection of the vesical neck was performed in all of the 7 cases in which the cysto-urethrogram disclosed evidence of increased tonicity of the external sphincter. Excellent results were obtained in 5 of the cases (the patients were able to empty the bladder

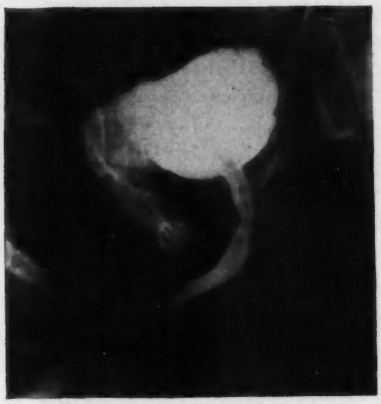

FIG. 5. Cysto-urethrogram showing apparent relaxation of external urethral sphincter in case of complete lesion of spinal cord.

completely). In the other 2 cases, the patients were unable to void despite repeated transurethral resection but were able to void well and empty the bladder while under any one of the three types of anesthesia. One of these cases has been reported in detail above (case 3). In the other case (fig. 7) the patient refused to undergo section of the lumbosacral roots and was dismissed with an indwelling catheter.

In 2 of the 3 cases in which there was either no evidence of increased tonicity or actual relaxation of the external sphincter, the lesion of the cord had been present for a relatively short time (6 to 8 months) and the patients had flaccid paralysis of the lower extremities without any apparent reflex spasm. The lesions were complete in each case. In 1 case, it was situated at the eighth thoracic vertebra and in the other it was situated at the tenth thoracic vertebra. There was no trabeculation of the bladder in either case. Each patient could initiate micturition at will by abdominal straining with no sign of automaticity and could empty

the bladder completely. In 1 case there was no loss of urine between voidings. In the other case, sudden movements or straining would bring about the loss of small amount of urine. The cysto-urethrogram in this case disclosed marked relaxation of the external urethral sphincter (fig. 5). The third case is of questionable value for this study as cysto-urethrograms were not made until after the

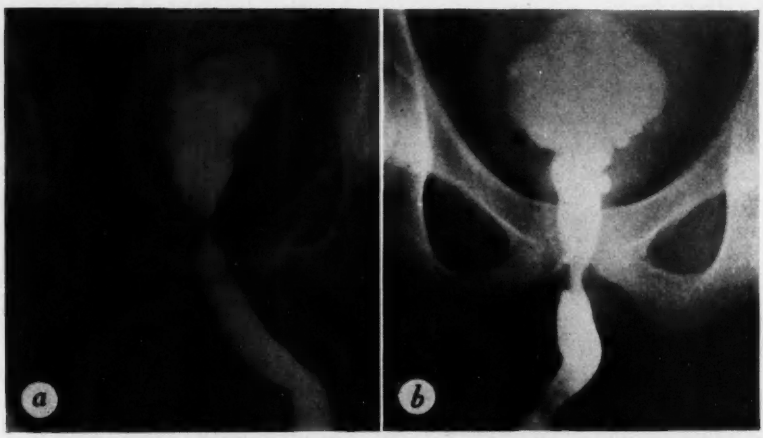

FIG. 6. Cysto-urethrogram of typical cord bladder (automatic type) in case of complete lesion of spinal cord; *a*, increased tonicity of external urethral sphincter before pudendal block; *b*, relaxation of external urethral sphincter during pudendal block.

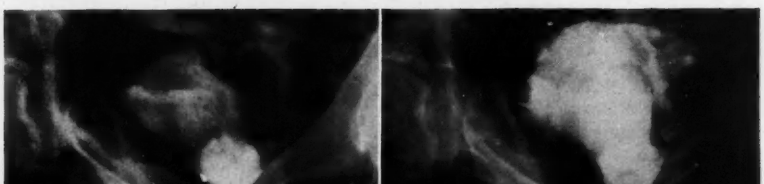

FIG. 7. Cysto-urethrogram of typical spastic cord bladder; *a*, increased tonicity of external urethral sphincter before pudendal block; *b*, relaxation of external urethral sphincter during pudendal block.

patient had secured an excellent result from transurethral resection of the vesical neck. (The operation was done before this study was undertaken.) In this case the lesion was situated at the eighth thoracic vertebra; it had been present for 6 years and was complicated by complete urinary retention which had required catheterization three times daily for 6 years. Flaccid paralysis of the lower ex-

tremities also was present in this case and there was no evidence of reflex spastic contractures.

INTERPRETATION OF DATA

It is obvious that the study of these 15 cases does not warrant any far-reaching conclusions. Nevertheless, some interesting speculations can be made. The results of this study suggest that the increased tonicity of the external sphincter may be a manifestation of the same process and exciting factors which cause increased tonicity of the detrusor muscle, trabeculation of the bladder and increased tonicity of the vesical neck. The study suggests that these changes may take a long time to develop in some cases (which would account for the fact that some patients who recover satisfactory vesical function a few months after the onset of lesion of the cord later have residual urine, infection and severe vesical dysfunction). The observations suggest that increased tonicity of the external urethral sphincter usually accompanies increased tonicity of the bladder and vesical neck. In an occasional case, however, it appears that weakness or relaxation of the external urethral sphincter may be associated with increased tonicity and trabeculation of the bladder and vesical neck (as for instance is observed in some cord bladders such as those caused by spina bifida and myelodysplasia in infants and children in whom incontinence may be present in the absence of residual urine). The observations also suggest that in most cases in which increased tonicity of the external sphincter is present, it is insufficient to interfere with the complete evacuation of urine after transurethral resection. In a few cases, however (as in case 3), the external urethral sphincter apparently may become so spastic as to cause obstruction. The hypertonicity of the external sphincter may also answer the question as to what provides continence in cord bladders after transurethral resection of the vesical neck.

It is also interesting to speculate as to the cause of the increased tonicity of the bladder and its sphincters in neurogenic vesical dysfunction. One might assume that the increased tonicity of the external urethral sphincter is the well-known response of skeletal muscle to a lesion of the upper motor neuron. On the other hand, one wonders if the extravesical spastic reflexes from the lower extremities and other muscles below the level of the lesion may be a contributing factor. This was suggested years ago by Head and Riddoch, who observed increased spasticity of the bladder with more frequent and irregular evacuations of urine when troublesome reflex contractions of the lower extremities were present.

We are of the opinion that this study has plotted some new avenues of therapeusis which warrant further exploration. In the case of the cord bladder in which trabeculation, increased tonicity and urinary incontinence are present but the bladder does not contain any residual urine, the treatment must be directed toward increasing the strength of the external sphincter and weakening the vesical neck. The latter is easily accomplished by transurethral resection. The former as yet is not possible except in cases in which the patients are women and plastic operations on the urethra, such as the Kelly operation, furnish a crude but sometimes satisfactory solution of the problem.

In the occasional case in which the hypertonic external urethral sphincter is sufficiently obstructive to prevent complete evacuation of the bladder, in spite of adequate transurethral resection of the vesical neck, several surgical procedures seem to be available: 1) bilateral section of the pudendal nerves, 2) intradural section of the roots (or anterior roots only) of the fourth and fifth lumbar and the first, second, third, fourth and fifth sacral nerves and 3) the intraspinal injection of alcohol as is being used at present in some Army and Navy hospitals to eliminate troublesome spastic contractures of the lower extremities without resorting to rhizotomy. Section of the pudendal nerves with treatment of neurogenic vesical dysfunction has been considered previously by others interested in this subject among whom are Nesbit and Webb, and Huggins, Walker and Noonan. Experience has been insufficient to determine which would be the better procedure.

The procedure of rhizotomy again brings up the situation which we called problem 3 in the beginning of this paper; namely, the problem of the irritable automatic bladder which has a small capacity and empties its contents completely (either with or without benefit of transurethral resection). In cases of this type, the intervals between evacuations of urine are so frequent and irregular that vesical function cannot be considered satisfactory. It has been demonstrated by Munro and other investigators that anterior rhizotomy of the lower thoracic and the lumbar nerves to eliminate troublesome massive reflexes and reflex contractions of the lower extremities often results in improvement of the automatic bladder by increasing its capacity and the time between evacuations of urine. It has been the practice, however, to preserve the integrity of the sacral roots in order to prevent the production of an autonomous (nonautomatic) bladder which is described as a type of vesical dysfunction most difficult to treat. As stated previously, it has been our experience with transurethral resection in cases of cord bladder that the autonomous (nonautomatic) bladder responds more easily to therapy than does the automatic bladder. Furthermore, the patient can initiate micturition at will and is not bothered by having to wait for the bladder to choose its own time for evacuation. After seeing the results in case 3, we would speculate that in selected cases in which an irritable automatic bladder is associated with reflex contractions of the lower extremities a better result may be secured if the rhizotomy includes the sacral roots as well. The resulting situation should then simulate that which is present when a lesion destroys the conus medullaris and cauda equina. When such a lesion is low enough to permit preservation of the abdominal muscles, the results of transurethral resection are usually excellent. It is our opinion that this procedure should be given a fair trial.

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MULLERIAN DUCT CYSTS[1]

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The small number of cases reported, including the few in which diagnosis was made preoperatively, confirm the fact that mullerian duct cysts are a rare urologic problem. Early authors may have been prompted to describe them as prostatic cysts because of the proximity of these growths to the prostate.

Changes in the mullerian duct produce these cysts, and in the case of masculine pseudohermaphrodism, degeneration of the mullerian duct does not occur. Instead of a cyst, there is formation of a complete uterus and fallopian tubes with an opening into the urethra at the usual location of the utricle.

Hallock described an orange-sized cyst, rectally palpable just above the prostate, presumably a cyst of Müller's duct; R. Campbell Begg reported a massive cystadenoma of Müller's duct; Coppridge presented a review of the literature and reported a case: that of a large, symmetrical cyst in the midline, arising from a remnant of Müller's duct. Hennessey added a description of a case to the short list of authenticated cases.

In 1944 Deming and Berneike presented a detailed review of the subject, and stressed the fact that there is a tendency, in the literature of prostatic disease, to include these mullerian duct cysts in the category of prostatic cysts. They outlined a group of diagnostic criteria to silhouette the disease, including clinical, histologic, and pathologic features which are characteristic of mullerian duct cysts.

CASE REPORT

The following is a report of a case which was diagnosed preoperatively and confirmed at operation:

Z. G., a male aged 41 years, married, Mexican descent, born and residing in California, was admitted to United States Naval Hospital, Long Beach, May 6, 1944. The chief complaints were attacks of purulent urethral discharge, urinary frequency, and dull aching pains in the left lower abdominal quadrant and rectum. He had attacks of bloody discharge from the urethra since June 1943, and more recently, a profuse purulent discharge which persisted for approximately 2 days. For 4 to 5 days prior to this urethral discharge, the pain in the left lower quadrant of the abdomen and in the rectum was more severe.

General physical examination revealed a well nourished male; abnormal physical findings were limited to lower left quadrant of abdomen, genitalia, and rectum. The penis, testes, vasa deferentia and epididymes were normal to palpation. Rectally, the prostate appeared normal in size, shape and consistency. Above the prostate, slightly to the left of the midline, was a tense, tender, pear-shaped cystic mass approximately the size of a lemon. Bimanual

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

examination of the lower left quadrant of the abdomen elicited tenderness; however, the mass could not be palpated suprapubically.

Prostatic smear was normal. Results in Kahn blood test were negative. Nonprotein nitrogen content of the blood was 28 mg. Stool examination showed negative findings. Blood count was essentially normal. Centrifugated specimen of urine showed a few red blood cells and many pus cells. Culture of urine was positive for staphylococci.

Proctoscopic examination revealed a well defined tumor mass approximately the size of a large lemon, apparently between the bladder and rectum. This mass did not involve the rectal wall. An attempt was made to tap the cyst with a lumbar puncture needle, introduced through the perineum, but proved unsuccessful.

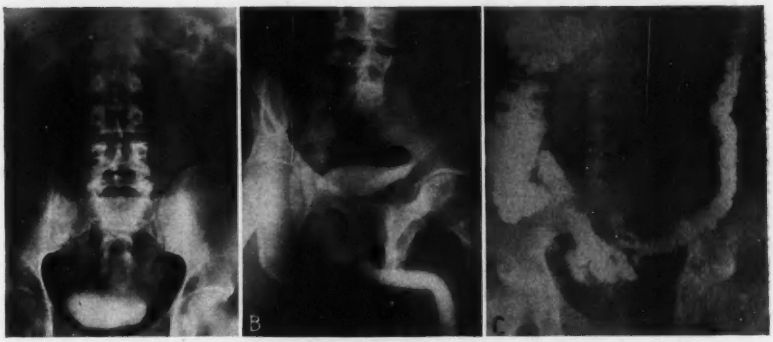

FIG. 1. *A*, Intravenous pyelogram. *B*, Cysto-ureterogram, lateral view. *C*, Roentgenogram taken after barium enema, showing normal sigmoid and rectum.

The next night the patient had a profuse urethral discharge, but the following day no discharge was present. After this the urine appeared grossly clear; the rectal mass was distinctly smaller; and the patient was free from pain.

Intravenous pyelograms showed no abnormality (fig. 1, *A*). Urethrogram showed a normal urethra. Cysto-ureterogram gave an entirely normal picture (fig. 1, *B*). Roentgenogram, taken after barium enema, revealed no significant findings (fig. 1, *C*). Cystoscopy showed a normal bladder except for elevation of the left half of the trigone with displacement of the left ureteral orifice toward the midline. Posterior portion of the urethra appeared normal. Jets of clear urine were observed from each ureteral orifice. Except for displacement of the left vesicle away from the midline (fig. 2, *A*, *B*), vesiculograms demonstrated normal seminal vesicles. The tumor was extravesicular and did not involve either seminal vesicle. Biopsy of specimen taken from an inguinal lymph node revealed a chronic inflammatory reaction.

Operation: Spinal anesthesia was used. Through a subumbilical, midline incision, the posterior wall of the bladder was exposed by removing the peritoneum by sharp dissection. Adherent to the posterior wall of the bladder was a thick-walled cystic mass about the size of a lemon. Considerable difficulty

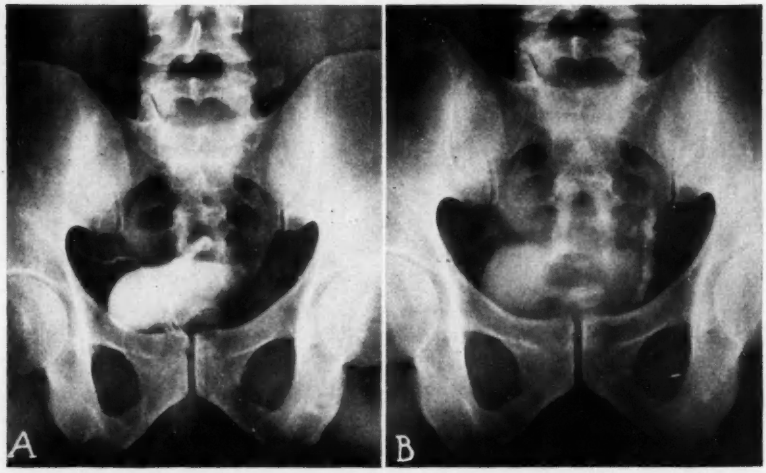

FIG. 2. *A*, Vesiculogram taken after injection of right seminal vesicle. *B*, Vesiculogram taken after injection of left seminal vesicle, demonstrating displacement of vesicle away from midline.

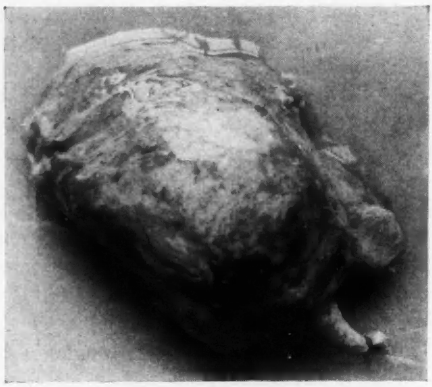

FIG. 3. Surgical specimen of mullerian duct cyst, showing ventral surface

FIG. 4. Surgical specimen injected with opaque medium, demonstrating thickness of cyst wall and outline of cavity.

was encountered in dissecting it away because of the vascularity of the tissues and firm attachment to the rectum. Both seminal vesicles and the vasa deferentia were dissected away from the cyst. The stalk of the cyst was traced to the prostatic portion of the urethra where its attachment was divided. The cyst was removed in toto.

The specimen measured 6 by 4 by 3 cm., and was cystic in structure. The dorsal surface was relatively smooth and reddish-grey in color; ventral surface rough and irregular, and adherent to it were strands of muscle fibers (fig. 3). There was a canal-like structure containing a lumen at one end which measured 1.5 by 0.3 cm. This canal was continuous, with a large, somewhat flattened oval cavity, and adherent to its grey inner surface was hemorrhagic, necrotic material (fig. 4). Smear of the cyst contents showed numerous pus cells and red blood cells, but no spermatozoa. The wall of the cyst averaged 0.3 to 0.6 cm. in thickness. The wall was composed of bundles of smooth muscle and fibrous connective tissue, but sections showed areas of mucosa to have been destroyed and replaced by necrotic tissue. The lining epithelium was cuboidal in type. The microscopic observations were consistent with the diagnosis of mullerian duct cyst.

SUMMARY

A detailed account of the ninth authentic case on record of mullerian duct cyst is presented.

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DISCUSSION

DR. REED M. NESBIT (Ann Arbor, Mich.): We are indeed fortunate that Dr. Emmett has extended the frontiers of our knowledge regarding neurogenic bladder in the way that he has contributed.

I should like to report again about a patient whom I spoke of a year ago at our meeting—the one whom Dr. Emmett referred to—for I have seen him recently, about a month ago, for a check-up examination. This young man had a cord injury, and a year ago or two after his recovery, in 1942, he was still unable to urinate at all. I was about to do a transurethral prostatectomy resection on him in order to facilitate the evacuation of his bladder, and examined him with a panendoscope and to my surprise, found nothing to resect. Therefore, one of my associates, at my suggestion, injected novocain into both of his pudendal nerves and he was able thereafter to evacuate his bladder completely.

Dr. Max Peet, our neurosurgeon, did a pudendal urectomy on this young man, because we found on subsequent examination that his other pudendal nerve, in fact, all of his opposite sacral nerves, had been completely destroyed at the time of his original injury, so this man had his one remaining pudendal nerve very carefully dissected and excised by Dr. Max Peet under local anesthesia. Thereafter he evacuated his bladder completely and without difficulty. He has the sensory components remaining.

He was operated upon in 1942. I saw him a month ago when he returned for a check-up examination. He has sired 2 children since operation; he ejaculates normally, although he said that he does not have what he would consider an entirely normal erection. I cystoscoped him, and he appears to have a normal bladder.

I think that this patient demonstrates conclusively, as Dr. Emmett has suggested, that occasionally patients having spasticity of the external sphincter might have relief by pudendal urectomy.

One other point I would like to bring up, and that is to mention the very ingenious possibility of correcting this same difficulty. Dr. Semans, one of our younger urologists, who now resides and practices in Atlanta, Georgia, suggested the possibility in this type of case that a perineal approach be made much after the manner used to perform radical perineal prostatectomy. He says it is an acknowledged fact that all patients after a radical perineal prostatectomy have a very weak sphincter so he has suggested that a complete dissection around the prostate and external vesical sphincter be made in this particular type of case in order to weaken the external sphincter to the extent that the individual would be able thereafter successfully and completely to evacuate the bladder. Whether he has performed this operation, I do not know.

DR. LOUIS ORR, JR. (Orlando, Fla.): You will recall Dr. Reed Nesbit's remark at Stockbridge last year that he wanted to add a little confusion to the already confusing subject of cord bladder. I would like to add a little more confusion to this confusing subject. It all hinges around a young infantryman I followed

around England and back to his home town of Orlando, Florida. This man was in the hands of the Veterans' Administration. He was about twenty-four years' old and had suffered a very severe gunshot wound of the sacrum, and I think the fifth lumbar segment. We got him out of the Veterans' Administration, and he was seen by a number of urologists. He came into my hands, and I assured the family that we could very probably relieve his difficulty of not being able to void by a transurethral resection.

While in England he had been on drainage, and prior to being shipped back to this country, he underwent a suprapubic cystotomy. I examined him and did a rather superficial neurological examination and thought certainly this man could be relieved by an adequate transurethral resection, which in due time was carried out. About 6½ or 7 gm. of tissue were removed. The catheter was removed on the third day. He stood up by the side of the bed and voided 2 ounces. I thought this was an excellent sign. Thereafter, until this time, he has voided not one single drop. To add to my unhappiness, the family came in 2 or 3 weeks later and brought this young man along, stating to me he was to be married shortly, but that now he was very much in the position of the young man from Ghent; there were no signs of anything after the sensation of ejaculation whatsoever, and what could I do about it.

I was a little bit nonplussed at that. In time to come, we had this man return to college. He was seen by several other urologists in the college town where he was, and in due course of time, I communicated with Reed Nesbit, thinking about the pudendal nerve injections. We had him go up to the university and see Dr. Nesbit and his neurological associates. They made very comprehensive tests and additional urological investigations. It was their opinion after all that was done that this man possibly had some tissue left on the anterior aspect of the vesical outlet, but there was very little tissue on the floor.

Now, we have this man who has gone through all these various phases; he has had an adequate resection, and he has had a satisfactory pudendal nerve blocking and still does not void.

I guess we should turn now to this new frontier which has been opened by Dr. Emmett, which I enjoyed the discussion of very much, and I hope through Dr. Emmett's confreres at the clinic my status quo in the community can be re-established.

Dr. Clyde L. Deming (New Haven, Conn.): I should like to show the slides of a müllerian duct cyst which Dr. Rusche referred to. This was a Spanish individual who complained of bloody urine. He was found to have a bleeding point in his posterior urethra, which we thought was coming from the verumontanum. The only complaint that he had was bloody urine without pain. He also had bloody ejaculations.

These slides are photographs of x-rays. We show the cystogram and injection of the cyst behind the bladder. This is a side view. This was a complete outline of the urinary tract showing the cyst.

This slide will show you the surgical specimen of the müllerian type cyst and the connection with the verumontanum here. The surgical specimen is shaped like a uterus. The vasa were very large, much larger than ureters, and thickened.

This man completely recovered in about 18 days, was drafted into the Army and has not had any more symptoms.

This unusual cyst is a cause for hematuria, and as far as I know, there is no other treatment than complete excision. We removed this similarly to Dr. Rusche's method, and feel that conservative procedure of any kind is out of the question and that surgical excision is by far the choice of treatment.

I wish to thank Dr. Rusche for presenting this subject.

DR. GEORGE C. PRATHER (Brookline, Mass.): I thoroughly enjoyed Dr. Emmett's presentation and always enjoy Dr. Nesbit's remarks.

Dr. Emmett talked so fast that I couldn't, with my slow mind, digest each and every sentence that flew by. There are so many variables when considering a patient with a neurogenic bladder induced by spinal cord injury that I think it is extremely difficult to evaluate any one method of treatment in a particular instance.

The external sphincter has been a great problem in patients and in experimental animals with spinal cord injury, Langworthy, of course, did a tremendous amount of work trying to figure out what happened to the external sphincter when the cauda equina of animals was transsected. I believe that he came to the conclusion that when there was difficulty with bladder evacuation after cauda equina injury in experimental injury, that the obstructing feature was not at the bladder neck or the prostatic urethra, but was due, as he called it, to urethral compression, not visualizing, as I recall, actual spasticity of the external sphincter, but the natural resistance of compression of tissue that is present in the region of the membranous urethra.

I have been interested in urethrograms and spinal cord injuries, and have kept an eye on the region of the external sphincter, finding considerable variation, but as Dr. Emmett has pointed out, in most of them the constriction of the urethra in its membranous portion remains just as he demonstrates, after spinal cord or cauda equina injury, at nearly all levels, and that raises the point as to what causes that remaining compression. I frankly do not know. Of course Charlie Huggins took a flier at pudendal resections with variable results some years ago in the manner that Dr. Nesbit has described. His results were quite variable, so that in military service we did not pursue that form of study or therapy.

I think Dr. Emmett's idea is worth pursuing, but one must be very careful, I should say, in the individual who has a partial lesion, because some of those individuals will, in time, regain a certain amount of muscular activity in their lower extremities and not be completely paralyzed. If in a situation of that kind one does a rhizotomy, the individual, of course, will never have any muscular activity below the level of the rhizotomy, and rhizotomies were hesitantly done in military service, because in not all cases could it be demonstrated whether the spinal cord injury was complete or not, and none of us, nor the neurosurgeons, wished to take the responsibility of doing a rhizotomy unless time or surgical aid had definitely proven that the spinal cord had been completely severed.

One thing I wish Dr. Emmett would do in conjunction with his studies would be also to evaluate the action of the detrusor muscle, because I cannot help believing that there are always two factors in bladder physiology: One, naturally, the activity of the bladder muscle; the other, the activity or possible obstruction in various segments of the urethra, and I believe before any of us, or whoever is fortunate enough to evaluate finally all the factors of bladder activity, we should include both the physiology of the bladder muscle and the disturbances that are in the urethra.

DR. JOHN L. EMMETT (Rochester, Minn.): I haven't much more to say. I apologize for talking so fast. I suppose it is a bad way to cut your paper down when it is hard to get it in in time.

I think Dr. Prather has made a very interesting summary there about the relationship between the detrusor and the vesical neck or urethra. After all, we have been glibly stating that the reason we resect the vesical neck is because the vesical neck is spastic. In some cases it is very definitely fixed, and there is hypertrophic muscle there, apparently, but I do not think anybody can say that that is the original situation, that it may not be the fact that at the time the cord lesion of the vesical neck is just not able to relax.

Dr. Braasch used to say this ectasia—was that the word you used to use?

DR. BRAASCH: That was the word Kenneth Walker used first, and I copied him.

DR. EMMETT: At any rate, all we know is that after a cord lesion, in spite of increased tonicity of the bladder, eventually you can't get the urine out through that vesical neck, and the only thing you can do is substitute one mechanism for another and remove it.

In the last issue of the *Journal of Urology*, you will notice that Ney, Auerbach and Hoen from St. Alban's wrote an article showing the enlargement of the prostatic urethra and suggesting that there is still another sphincter. I can't quite visualize that. It does illustrate one point that possibly spasticity of the external sphincter of that region is one of the things that produces this bulbous enlargement of the prostate. Sometimes you have this contraction of the vesical neck; other times it is wide open.

About Dr. Louis Orr's suggestion, he has there an ambulatory patient apparently with good abdominal muscles, and yet can't empty the bladder. That is a rather interesting situation. He has only resected him once. That is the only criticism that I have of that, that in about 50 per cent of our cases we have had to resect them twice, even though we couldn't see anything more to resect.

I am wondering if maybe the patient shouldn't be resected again even though you can't see anything, and cut just a little deeper. I resect some patients 4 times. I have a girl that I resected 8 times in the course of a year and finally removed 16 gm. of tissue from her, and she is finally able to void. I took out 2 or 3 gm. each time, until there is only about two-thirds of a centimeter left.

In Dr. Orr's case, possibly one should think about investigating the external sphincter, but I would think before that, maybe further resection should be tried.

It is just one of those cases that you resect because you think it is there, and not because you see it.

Dr. Carl Rusche (Hollywood, Cal.): I wish to express my appreciation to Dr. Deming for his discussion and brief review of his case with the presentation of the surgical specimen. Shortly before examining the patient, I had reviewed his article on "Classification and Differential Diagnosis of Cysts of the Deep Male Urethra." Therefore, the preoperative diagnosis of müllerian duct cyst in this case was not difficult.

SURGICAL ASPECTS OF BILATERAL FAMILIAL PHEOCHROMOCYTOMA[1]

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The clinical syndrome of paroxysmal hypertension has always been a fascinating diagnostic problem, and its association with tumors arising from the medullary portion of the adrenal gland—pheochromocytoma or paraganglioma—has been recorded many times in the literature. During the past year 2 cases of this syndrome have been studied and operated upon at the Johns Hopkins Hospital. These cases presented such unusual features that a report on the surgical aspects of the problem should be recorded. The diagnostic studies were carried out by Drs. Evan Calkins and John E. Howard of the Department of Medicine who have also made an extensive study of the available world literature on the subject. With their permission I shall quote extensively from their article with a discussion of some of the surgical problems which arose in the management of these cases.

First of all, in the study of these individuals was the interesting fact that they were blood relations—aunt (R. L.) and niece (M. M.)— and that the latter's mother and the former's sister had died at the age of 28 from hypertension, which had manifested itself by symptoms very similar to those presented by both of our patients. A second feature of extreme interest is the fact that both patients suffered from bilateral tumors which were successfully removed by surgical operation, and in 1 case (M. M.) 3 such tumors—one recurrent after previous operation—were excised. These are the first cases in the literature from which bilateral tumors have been successfully removed, and M. M., from whom three pheochromocytomata have been excised, will probably remain unique.

Calkins and Howard found reports of 176 pheochromocytomata in the world's literature, "but only 47 of them were proven to be endocrinologically active by cessation of symptoms following surgical removal." They also found "15 cases of bilateral pheochromocytomata in which the tumors were located in or near the adrenal glands, and 2 cases each with tumors arising in Zuckerkandl's body and the retroperitoneal ganglia.

"It should be emphasized that no surgical attempt was made to remove the tumors in any of these cases. There is no proof, therefore, that the pheochromocytomata were actively secretory and responsible for any of the patient's symptoms, though in many instances it seems altogether likely. Insofar as we are aware, the patients here reported are the first from whom more than one pheochromocytoma has been removed. MacKenzie, in discussing a paper by Hyman and Mencher, mentions a patient of his own whose paroxysmal hypertension disappeared after removal of a tumor. Four and a half years later the symptoms recurred. Though careful exploration of both adrenal areas failed to reveal a

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 5, 1947.

tumor, MacKenzie was of the opinion that another pheochromocytoma existed somewhere."

Malignant tumors arising from the medullary portion of the adrenal gland have been reported, and it is an important fact that of the 17 cases of bilateral pheochromocytomata which Calkins and Howard found recorded in the literature, 5 were found to be malignant, and in none of these cases were symptoms of paroxysmal hypertension present. In 15 of the cases of multiple tumors, pheochromocytomata were located in or near the adrenal glands, and in 7 the patients were known to have suffered from constant hypertension. In these 7 cases the tumors were benign. Up to the present no case of malignant tumor associated with the clinical syndrome of paroxysmal hypertension has been reported, but McKenna and Hines in 1935 reported a case with precordial palpitation and blood pressures ranging from 160–190 from which a tumor, microscopically malignant, was removed. The patient died 2 years later of metastases.

Of the 10 cases of benign bilateral pheochromocytomata reported, 7 contained information on blood pressure, and all these patients had hypertension. McGavack records his impression that patients with malignant tumors have normal blood pressure.

PATHOLOGY

Pheochromocytomata are usually well encapsulated though the capsule may be thin and delicate. On section the tumor is soft and has a characteristic reddish brown appearance. In the benign types areas of hemorrhage, necrosis and calcification may be present, but are more frequently seen when malignant changes have occurred. The adrenal gland is often compressed and flattened, especially in the larger tumors, and may be partially incorporated in, or densely adherent to the capsule of the tumor.

Microscopically many large anastomosing venules and sinusoids are present, especially in the central portion of the tumor. The tumor cells are arranged in fairly large groups and cords of irregular shape, between which there are delicate connective tissue septa with capillaries.

The individual cells are rather large and polygonal, and do not vary much in size or appearance. The cytoplasm is coarse and granular and often contains basophilic and eosinophilic granules. The pheochrome properties of the cells are evidenced by their hazy brown color. The nuclei are usually rounded or oval and most are hyperchromatic, some with large nucleoli. In general the tumor cells more closely resemble ganglion cells than the chromaffin cells of the normal adrenal medulla.

SYMPTOMS

In the typical case of paroxysmal hypertension the patient suffers from sudden episodes, usually characterized by severe generalized headache associated with blanching, particularly around the mouth, and cold extremities followed by generalized flushing and a sensation of warmth. The characteristic diagnostic feature is a rapid rise of blood pressure. Before the episode the pressure usually

is at normal levels, but with the onset of the attack both systolic and diastolic rise rapidly within a few minutes, often to astonishingly high levels. As the attack diminishes in intensity, the pressure returns to its previous normal level. The episodes usually last for 5 to 15 minutes, are often accompanied by nausea and vomiting and fainting spells with momentary unconsciousness. During the episode there is a feeling of marked anxiety and apprehension, and following it marked lassitude and complete exhaustion. With the course of the disease the episodes become more frequent and more severe, and death may occur in one of the crises, either from acute myocardial failure or from a cerebral accident. The episodes may be brought on by lying in a certain position, particularly on the side in which the tumor is located, by straining at stool and by emotional crises, such as anger or sudden fear.

DIAGNOSIS

When a patient presents the above symptom complex, the probability of the presence of a pheochromocytoma should be strongly suspected. These tumors may also be found in cases of sustained hypertension. Smithwick reports 2 cases in which, in the course of operative exposure for the purpose of sympathetic ganglionectomy for essential hypertension, pheochromocytomata were found, after the removal of which the blood pressure returned to normal limits. The diagnostic difficulties in such cases are obvious, and as yet a correct preoperative diagnosis has not yet been reported in a case of sustained hypertension due to the presence of a pheochromocytoma.

When the clinical picture is suggestive of the presence of a pheochromocytoma, radiographic studies should first be carried out. In the flat film and intravenous urogram in some cases a soft tissue shadow may be visualized in the adrenal area, and the corresponding kidney may be displaced downward, but in many cases, particularly when a small tumor is present, no significant information can be obtained. If satisfactory intravenous urograms are obtained, no further information of value can be expected from retrograde pyelography.

Perirenal air or oxygen insufflation has been recommended as a valuable diagnostic procedure, particularly by Cahill. That this technique is of great value in many cases is without question, but often the results from a diagnostic standpoint are equivocal and great difficulty in the correct interpretation of the films may exist. Furthermore, the literature on this subject contains reports of sudden death from air embolism, probably due, it is true, to faulty technique. Nevertheless, the possibility of a tragedy resulting from what should be a minor diagnostic procedure cannot be ignored with temerity. In the 2 cases which are the subject of this report, the particular side on which the tumor was located was inferred from the law of probability in case 1 because at previous operation a portion of the capsule could not be removed, and it was therefore considered that recurrence of the original tumor was the most probable cause of the recrudescence of her symptoms. It is quite possible, however, that if perirenal insufflation had been carried out and clear-cut films obtained, the presence of bilateral tumors—one recurrent postoperatively—could have been recognized.

In case 2 the tumor in its capsule, together with the kidney, had been removed so that a tumor of the opposite adrenal was considered the most likely possibility.

In 1945 Roth and Kvale described a tentative test for pheochromocytoma. These observers found that by an intravenous injection of 0.05 mg. histamine base in 3 patients with pheochromocytoma the blood pressure "rose approximately 100 mm. more than the elevation obtained by the cold pressor test and was accompanied by the characteristic symptoms of a typical spontaneous attack."

Calkins and Howard state that "our experience with the use of the Roth-Kvale test coincides closely with theirs. In our patients the injection of histamine produced an abrupt rise in blood pressure, which dwarfed that which accompanied the cold pressor test. The drug seemingly induced episodes which were in all respects identical with spontaneous attacks. The test appears to have a two-fold value, first as a method of producing attacks at will for study, and, second, as an indication of the presence of pheochromocytoma. In the patients here reported, so long as the test remained positive, it was possible to find and remove more tumors. Conversely, so far as known, no pheochromocytomata have been found in patients in whom the test was negative."

From the foregoing the great value of this simple test is obvious. In our two patients severe attacks of paroxysmal hypertension were induced by the injection of histamine, but these attacks were no more severe than some of the spontaneous episodes. The great value of the test as a diagnostic procedure would certainly seem to outweigh any possible dangers.

SURGICAL PROBLEMS

When a diagnosis of probable pheochromocytoma has been tentatively made, and the side on which the tumor is located has been determined as accurately as possible in accordance with the foregoing, it is obvious that an attempt to remove the tumor surgically should be undertaken as soon as possible in order to spare the patient from the hypertensive crises, any one of which might conceivably terminate in a fatal outcome. These tumors are usually well encapsulated, but the capsule is often quite thin and may tear easily so that great care should be taken during the surgical procedure to avoid this accident. If a previous operation has been performed, the resulting scar tissue may greatly complicate the enucleation and enhance the danger of tearing the capsule.

The adrenal gland is usually found flattened out, compressed and either adherent to, or partially incorporated in the capsule. In many cases excision of the entire adrenal has been carried out to ensure complete removal of the tumor without injury to its capsule. The possibility that the adrenal on the opposite side may be absent or if present that its function might be insufficient to sustain life cannot be ignored so that, if technically possible, as much as possible of the adrenal tissue must be conserved. In Case 2 we were faced with the fact that the entire left adrenal gland with the tumor and the kidney had been removed at the first operation. On exposure of the tumor on the right side about two-

thirds of the adrenal gland was found so intimately incorporated in the capsule of the tumor that to preserve the gland in its entirety, it would have been necessary to leave behind some of the capsule of the tumor. However, it was possible to separate about one-third of the adrenal with intact blood supply from the tumor. A clamp was placed across this portion of the adrenal as close to the capsule of the tumor as possible, and the latter was then excised leaving behind about one-third of the adrenal, normal in appearance and with intact blood supply. In spite of the obvious hazard that this small remaining portion of the gland would be inadequate to support life the clinical picture and the findings at operation were such that this course was deemed justifiable.

The blood supply of these tumors comes mostly from the adrenal gland itself, though some operators have described a vascular pedicle arising independently from the great vessels above the origin of the main vessels supplying the adrenal. In our own three operative experiences no such definite pedicle was encountered, and hemorrhage was controlled by clamping individual vessels as they were encountered in the enucleation.

The choice of surgical approach is most important. It is axiomatic, of course, that the exposure must be adequate to enucleate the tumor in its capsule in such a manner that the blood supply will be under direct vision so that its control can be assured. In our three operations the lumbar approach was chosen in each case, and from the previous operative procedures we inferred according to the law of probability the side on which the tumor was located. It must be admitted, however, that in case 1 the possibility of a tumor on the unoperated side had not been sufficiently considered at the first operation.

To ensure adequate exposure the twelfth and eleventh ribs were resected at each operation. By this technique in each instance an excellent exposure of the whole tumor was obtained so that complete removal of each tumor was possible and the blood supply satisfactorily controlled. It was felt in each instance that without resection of the last two ribs complete removal of the tumor would have been impossible or at least extremely hazardous. It will be noted, however, that in each operation, either in the course of the rib resection or in the actual enucleation of the tumor, the pleura was opened. In spite of prompt closure of these accidental injuries, pneumothorax was a disturbing postoperative complication. Fortunately prompt and efficient medical care was available so that these patients were carried through their complications without serious difficulty.

Injury to the pleura might conceivably be avoided by more meticulous operative technique, but this accident must be considered in all operations for the removal of adrenal tumor through a lumbar exposure. In a review of the literature, one is struck by the high incidence of pleural injury by surgeons using a lumbar incision.

In recent years the writer has been impressed with the excellent exposure afforded by the transverse abdominal incision in which the rectus fascia and both recti muscles are completely cut across. This operative approach has been found most adequate for such procedures as simultaneous bilateral ureterosigmoidos-

tomy. The satisfactory healing which occurs without postoperative hernia has been most striking, and in cases of ureterosigmoidostomy we have no hesitation, when the first incision has healed, in making a second, lower transverse incision for cystectomy in cases of extensive malignant disease of the bladder.

On numerous occasions the exposure of both adrenals, which can be obtained by an upper abdominal transverse incision, has been observed in the course of operations on upper abdominal viscera by general surgeons. Although I have had no personal experience with this approach for the removal of adrenal tumors, the exposure has seemed completely adequate for this procedure. This incision in the case of suspected pheocyromocytoma would make perirenal insufflation entirely unnecessary, and if a tumor should be found the surgeon would have the additional comfort of a complete visualization of the opposite side, and thus be able to assure himself as to the condition of the adrenal gland on that side in case the situation made necessary the removal of the entire adrenal on the side where the tumor was located.

Biskind, Meyer and Beadner (1941) collected 29 operations for the removal of pheochromocytoma with 4 operative deaths, and 1 death 30 days later from pneumonia. In 12 cases the transperitoneal approach was used. In 8 of these cases severe shock was recorded, and 3 patients died as a result of the operation, and one, 30 days later from pneumonia. In 4 cases there was no shock at the end of operation, but one developed pneumonia subsequently with wound infection, but recovered.

We were able to find 11 cases, including our own 3 operations, in which the lumbar approach was used. In 5 of these no shock occurred at operation, although in one pneumonia subsequently developed. In 2 cases slight shock occurred, and in 4 cases severe shock, but there were no operative deaths. Although this series is too small for any accurate comparison of the operative approach, the lack of mortality and the fewer cases of severe shock when the lumbar approach was used is significant. This might be explained by the more adequate exposure of the tumor, especially when the eleventh and twelfth ribs are resected, and hence more accurate control of hemorrhage. The frequency with which the pleura is injured in the lumbar approach, however, cannot be disregarded. One of the great advantages of the transperitoneal approach, however, lies in the fact that both of the adrenal glands can be exposed.

CASE REPORTS

Case 1. M. M. (No. 382786), a 22 year old white female, entered the Johns Hopkins Hospital on April 19, 1946. She complained of recurrence of symptoms which had been relieved for a 9 months' period by an operation performed 4 years previously at another hospital. Her mother had died with hypertension at the age of 28, having experienced symptoms quite similar to those of which the patient complained. M. M.'s past history included diphtheria, scarlet fever, ruptured appendix and a dislocated hip, all prior to adolescence. Six months before the onset of her present complaints there had been an illness of

2 weeks' duration, with headache and stiff neck, which she was told was poliomyelitis. There was apparently complete recovery. Menstrual periods had always been regular and the flow normal.

Four years before our observation began, the patient was seized suddenly, while in bed, with a violent generalized headache which lasted only 10 minutes. During the ensuing 3 months similar attacks recurred at approximately biweekly intervals. These episodes were accompanied by blanching and coldness of the extremities and were followed by flushing and a sensation of warmth, without conspicuous sweating. Because of these symptoms, she entered a hospital in New York where an operation was performed with removal of a pheochromocytoma from the left adrenal region. Studies performed and the procedures carried out at that time were fully reported by Hyman and Mencher. The authors were aware that, at operation, the posterior layer of the capsule of the tumor was left in situ, because it was adherent to the surrounding structures.

Following operation the patient had no more attacks for a period of 9 months, after which time the attacks recurred and she began to experience "brief periods of over-fatigue, complete lassitude, tremors, palpitations and alternate blanches and flushes. At first these spells were infrequent, but more recently have been daily occurrences. Within the past month I have had several headaches similar to those in the preoperative period, together with fainting spells and nausea. I am unable to feel completely healthy for even one entire day."

At the time of admission the attacks were occurring several times a day. They commenced apparently spontaneously, although they were especially apt to occur when the patient was at stool or lying in bed on her left side. Heralded by severe generalized headache, they were climaxed by marked blanching and nausea and sometimes vomiting. Occasionally the patient became momentarily unconscious. After about 3 minutes she experienced great warmth, sweated and was left exhausted, the whole episode lasting about 5 minutes.

Physical examination in a resting state revealed a healthy appearing girl of 22. The skin was warm and slightly moist. Pupils were normal, and there were no visible abnormalities in the fundal vessels. The thyroid was diffusely and symmetrically enlarged to about twice average size. Neither thrill nor bruit was present. Heart rhythm was regular, rate slightly rapid. Although the apical impulse was accentuated, there were no evidences of cardiac enlargement. No significant murmurs were heard. Blood pressure was 120/80. The rest of the physical examination was normal.

During attacks she became markedly pale, especially in the extremities and around the mouth. "Goose pimples" might be apparent. An expression of great anxiety appeared, and on occasions she vomited. The blood pressure reached a maximum of approximately 200/150, but neither the cardiac nor the respiratory rate was much affected. Following the climax, she would become violently flushed, perspire freely and sink exhausted to the bed. The blood pressure did not return to normal for about 10 minutes.

On plain x-ray film the outline of the right kidney was clearly seen, normal in size and position; no suspicious shadows in kidney or ureter, contour smooth.

No suggestion of soft tissue mass was seen above the kidney. A portion of the twelfth and eleventh ribs on the left side had been resected. The outline of the kidney was clearly seen, normal in size and position; contour smooth. No suspicious shadows were seen in kidney and ureter. Above the kidney, beneath the eleventh rib, there was a suggestion of a soft tissue mass, measuring about 4 by 2 cm.

The intravenous urogram showed good excretion of dye in both kidneys. In the 15 minute film the pelvis of the right kidney was well filled, no dilatation, distortion, filling defect or obstruction at the ureteroplevic junction. The calyces were clearly defined, cup-shaped and showed no distortion. The pelvis of the left kidney was well filled, no dilatation, distortion, filling defect or obstruction at ureteropelvic junction. The calyces were clearly defined, cup-shaped and showed no distortion.

The complete laboratory data and special studies are given in full in Calkins and Howard's report, so that only the significant findings and tests will be briefly described here. The cold pressor test produced a rise in blood pressure from 125/70 to 140/100 without symptoms. When 0.05 mg. histamine base in 1 cc normal saline were rapidly injected into the brachial vein, there was a momentary flush, and then an almost instantaneous rise in blood pressure from 140/80 to 200/140. This elevation in blood pressure was associated with a reproduction of all the symptoms and signs of the spontaneous attacks. The test was definitely interpreted as positive. When 0.5 mg. epinephrin were injected subcutaneously, a 20 per cent rise in the systolic pressure occurred, but there were no subjective symptoms.

It was definitely concluded from the above findings that an excess of endocrinologically active chromaffin tissue was present. In the description of the previous operation, it was frankly stated that some of the capsule had been left behind at the previous operation. It therefore seemed most probable that a recurrent tumor was present on the left side, which previously had been operated on.

May 10, 1946, operation was carried out under spinal anesthesia and pentothal. The incision was commenced over the tenth rib at the border of the erector spinae muscles, carried downward and outward over the eleventh rib, about 1 inch above the scar of the previous operation. The eleventh and twelfth ribs were freed from the scar tissue and periosteum and resected close to their articulation. The incision was then carried through the muscles and scar tissue below the pleura, which was clearly visible, carried downward through the lumbodorsal fascia and upward, incising the costovertebral ligament and downward, avoiding the peritoneum. Gerota's capsule was opened and the kidney, which was surrounded by considerable scar tissue, was retracted downward. Above the upper pole of the kidney a soft, vascular tumor measuring about 7 by 4 cm. was found. The adrenal was flattened and stretched out across the tumor, and seemed intimately associated with its capsule. On delivering the tumor there was a rise of blood pressure to 240; the pulse became weak and rapid. A vascular pedicle on the mesial surface of the tumor was clamped, transfixed and ligated with black silk. It was possible to separate a

portion of the adrenal from the capsule of the tumor. This was clamped and tied, and about two-thirds of the adrenal removed with the tumor. The stump of the adrenal was transfixed with black silk. On exploration a small nick in the pleura was found, and was closed with fine black silk. The wound was closed in layers in the usual way, without drainage.

The patient left the table in poor condition, obviously in severe shock. During the manipulation of the tumor the blood pressure rose to 240. At the end of the operation it had fallen to 140. The pulse was rapid and weak, and a considerable amount of blood had been lost.

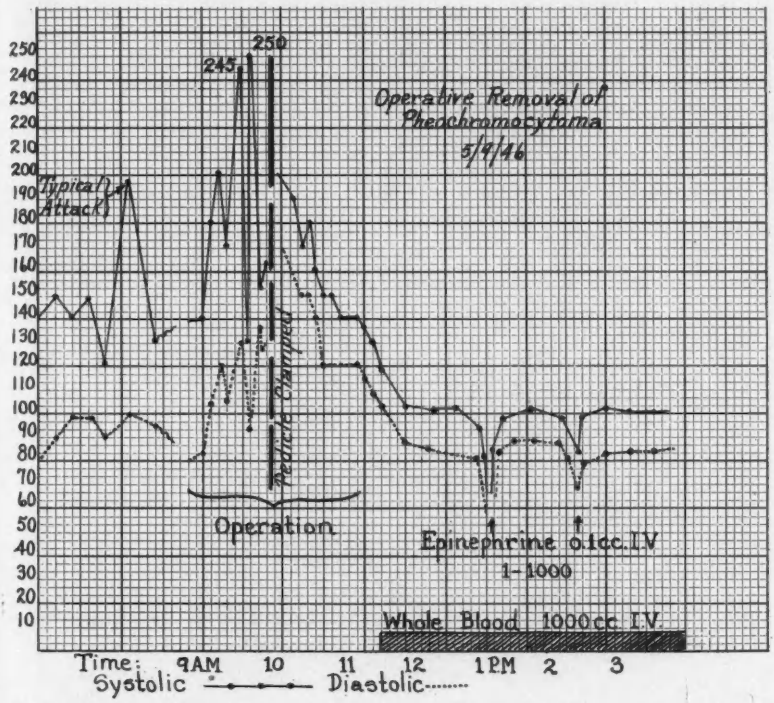

FIG. 1. Case 1. Chart, showing typical hypertensive attack before operation (probably psychic), operation, and immediate postoperative course.

Following operation the blood pressure continued to fall until it reached 80 systolic. Epinephrin, 0.1 cc, was injected intravenously, and a similar dose given 1 hour later. After this the blood pressure remained stable at 100/80 (fig. 1). A litre of whole blood was also administered after operation.

The gross specimen consisted of a bisected piece of tissue 5 by 4 cm., roughly oval in form and covered by capsule, along one side of which ran a thin ridge of yellowish tissue, which, on section, appeared to be a piece of adrenal showing cortical and medullary substance (fig. 2). A large oval tumor was situated at one end of the adrenal and seemed to be continuous with the cortex.

Microscopic section consisted of a piece of tissue at one end of which there was adrenal tissue composed of cortex and medulla, normal in appearance (fig. 3,*A*). The cortical cells themselves contained a great deal of lipoid. Attached to this was a piece of tissue which was composed of large cells with vesicular nuclei, arranged in an acinar pattern. Their nuclei were generally of the same size and shape. The cells contained a great deal of brownish pigment. There was very

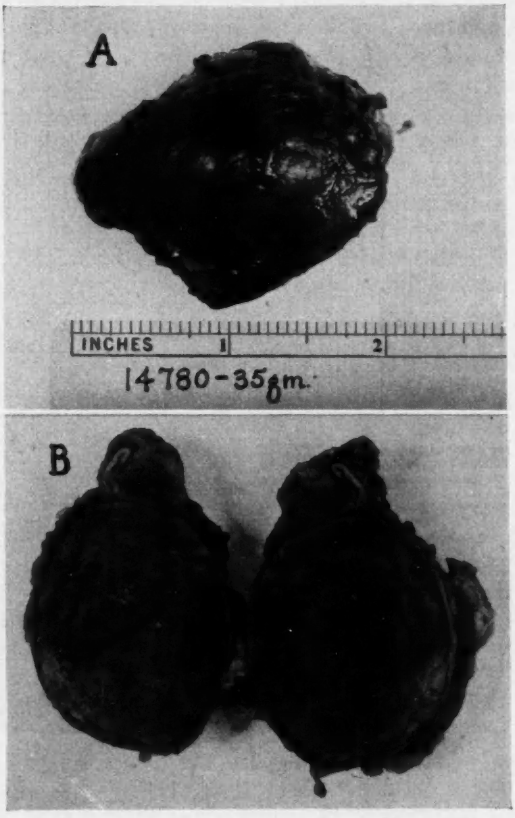

FIG. 2. Case 1. *A*, Tumor removed at first operation. *B*, Tumor bisected. Above and attached to lower pole can be seen cross section of portion of adrenal gland, which is grossly normal in appearance.

little mitosis or pyknosis present. The tumor was encapsulated by a thickened fibrous capsule which showed many infiltrations of cells resembling lymphocytes (fig. 3, *B*). Diagnosis: Pheochromocytoma.

On the day after operation signs of left pneumothorax and mediastinal emphysema were apparent. Cyanosis and respiratory difficulty which accompanied these complications were controlled by administration of oxygen. The respiratory problems disappeared after the third day. At this time phlebitis of the

right anterior tibial vein became evident at the site of the continuous intravenous injection.

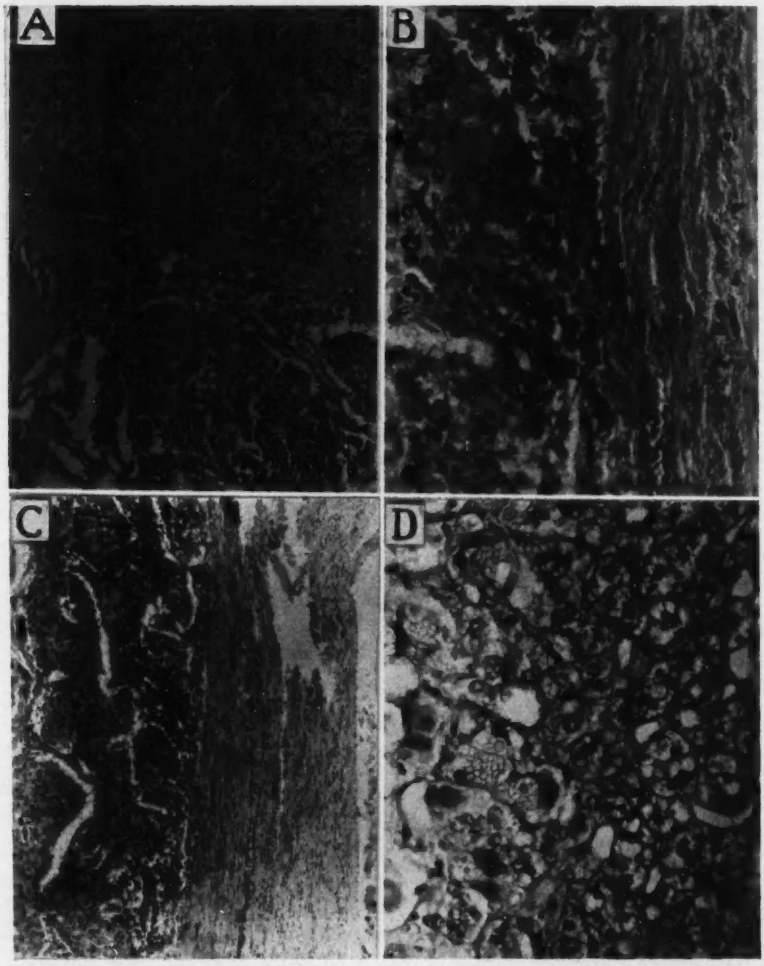

FIG. 3. Case 1. First operation. *A*, Low power photomicrograph, showing typical pheochromocytoma with fibrous capsule, which shows no invasion of tumor tissue. Above capsule can be seen normal adrenal cortical tissue. *B*, First operation. High power photomicrograph, showing typical pheochromocytoma with well defined fibrous capsule. There is no invasion of tumor tissue in capsule. *C*, Second operation. Lower power photomicrograph, showing typical pheochromocytoma with well defined fibrous capsule. There is no invasion of tumor cells in capsule. *D*, Second operation. High power photomicrograph, showing high lipid content of tumor cells with vacuolation and numerous fat droplets.

On the tenth postoperative day the patient commented that she felt "woozy" when she lay on her left side. Since this position had evoked attacks before

operation, blood pressure measurements were recorded with the patient in the left lateral decubitus. Upon assumption of this position, the blood pressure fell from 130/90 to 90/60, but 90 seconds later the patient exclaimed: "Here it comes!" The blood pressure rose precipitously to 240/170; and the patient complained of nausea and headache, weeping pitifully because she was having another attack after a second supposedly successful operation. As the blood pressure reached its peak 2 minutes after the attack began, there developed flush and profuse sweat and the pulse rate rose to 120, remaining elevated for several hours after the pressure had returned to normal.

Spontaneous attacks of this sort continued to occur when the patient lay on her left side, and sometimes when she assumed the upright position. Intravenous histamine test was repeated (this time using only 0.0125 mg. histamine base), and a typical attack resulted, the blood pressure rising to 210/130. Immediately prior to this test the blood sugar was 118 mg. per cent and the serum phosphorus 4 mg. per cent. Because of the continuing attacks and the positive histamine test, the conclusion was reached that there existed another pheochromocytoma.

The patient was discharged June 1, 1946 and returned on September 23. Meanwhile the attacks had occcurred less frequently but more severely than before.

The physical examination showed the same findings as the first admission. A spontaneous attack was observed 2 days after admission, the blood pressure rising to 220/135. From the clinical picture with recurrent attacks of paroxysmal hypertension and a definitely positive histamine test, it was decided that endocrinologically active chromaffin tissue was still present. As the tumor had been completely removed from the left side without injury to its capsule, it seemed scarcely conceivable that a recurrence could have taken place in this time, especially also in view of the fact that the histamine test was positve 10 days after operation. It was therefore decided that the tumor must lie in the right adrenal area.

A plain x-ray film showed the outline of the right kidney clearly. It was normal in size and position. The contour was smooth. No suspicious shadows were seen in the kidney or ureter. There was nothing to suggest a soft tissue shadow above the kidney. The outline of the left kidney was fairly well seen. It was normal in size and position, and the contour smooth. No suspicious shadows were noted in the kidney or ureter, and there was no evidence of soft tissue shadow above the kidney. The twelfth and eleventh ribs had been resected. A mild scoliosis was present, but the bones were normal.

An intravenous urogram showed excellent excretion of dye from both kidneys (fig. 4). The pelvis of the right kidney was well filled; no dilatation, distortion, filling defect or obstruction at the ureteropelvic junction; calyces cup-shaped and normal. The pelvis of the left kidney was well filled; no dilatation, distortion, filling defect or obstruction in kidney or at ureteropelvic junction.

On September 28, 1946, under ether anesthesia with pentothal induction, an incision was made at the level of the tenth rib, and carried down below the

anterior superior spine. The periosteum over both the twelfth and eleventh rib was mobilized, and the ribs resected close to their articulations. Gerota's fascia was then opened, and a normal kidney found. Above the kidney, in the region of the adrenal, a soft mass measuring about 8 by 6 cm. was exposed, which was freely movable. A small tear which occurred in the pleura was closed with silk. The tumor was then delivered into the wound. During this manipulation the pressure rose to 260/120. The adrenal gland was found compressed and thinned out, and intimately associated with the capsule. However, it was possible to separate about one-third of the gland from the capsule, and this was

FIG. 4. Case 1. Intravenous urogram taken previous to second operation. Pelvis and calyces of each kidney are well filled, clearly defined, and there is no distortion. Contour of right kidney clearly seen, and no suggestion of soft tissue shadow can be seen above kidney. On left side, twelfth and eleventh ribs have been resected, and upper pole of kidney is not clearly outlined, probably because of postoperative reaction.

clamped and transfixed, leaving intact the blood supply. The tumor was then delivered, but the capsule was ruptured, and some tissue was extruded. This was immediately swabbed out of the wound. Some vessels coming into the upper medial aspect were clamped and tied, and another blood supply posteriorly was similarly controlled. The tumor then, with its blood supply controlled, and about two-thirds of the adrenal gland attached to its capsule, was removed. The wound was then carefully sponged out to remove any tumor tissue which had extruded from the tear in the capsule, then washed out with ether. The wound was closed in layers with silk.

The patient left the table in good condition. During manipulation of the tumor the pressure rose to 240/120, but at the end of operation was stabilized at 140 (fig. 5). A transfusion was given during the operation. During the subsequent 4 hours after operation the blood pressure fell to 85/50. Epinephrine chloride, 6 mg., was administered during the first 5 hours and maintained the blood pressure at a normal level.

Pathological examination: The specimen consisted of an irregular mass of

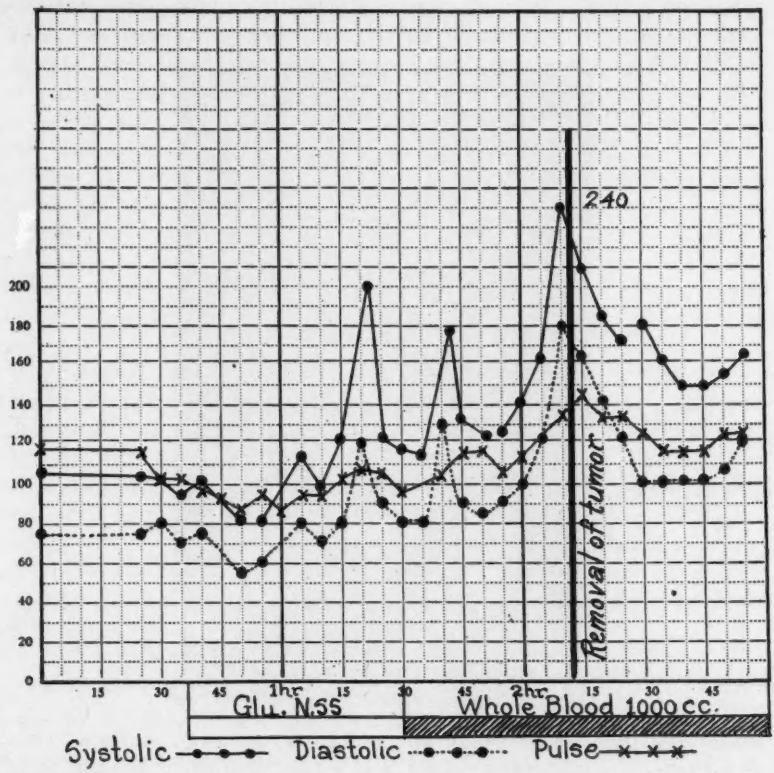

FIG. 5. Case 1. Second operation. Chart of immediate preoperative, operative, and postoperative course, showing typical hypertensive crisis occurring just before onset of operation (probably psychic).

tissue measuring about 8 by 10 cm. which was encapsulated, and a piece of adrenal tissue was apparently associated with the capsule. On section the compressed adrenal tissue looked normal. Section of the tumor itself showed a characteristic brownish apperance. (The tumor was sent to the laboratory for biological assay, so no illustration is available.)

On microscopic section a small piece of normal appearing adrenal was present, the medulla of which was continuous with the tumor growth which had a rather wild appearance with undifferentiated cells. Many large cells were present.

There was little or no apparent pigmentation. In some instances the tumor cells appeared to be within the blood vessels. Surrounding the tumor was a fairly thick capsule (fig. 3,*C* and *D*).

The postoperative course was complicated by fever and respiratory difficulty due to pneumothorax, which required tapping. Convalescence was otherwise uneventful, although a low grade fever persisted for several weeks.

The preoperative diagnostic procedures and postoperative follow-ups are shown in figure 6. The chart was prepared by Calkins and Howard. It will be seen that a definite positive histamine test was present 19 days after the first operation. Following the second operation on September 28, 1946, this test became negative and has remained so to date.

The patient was discharged on October 27, 1946.

She returned for examination April 23, 1947. She had felt quite well and had completely regained her strength, and for the last few months had been at work in her old occupation as welfare worker in New York City. She had had none of her previous attacks. A small draining sinus persisted at the site of the operation for several months after discharge, but had now completely closed.

General physical examination was negative. The blood pressure was 118/80 in the right arm and 115/80 in the left arm. EOM were normal. Pupils reacted. Fundi were clear. There was slight nasal obstruction on the left. The pharynx was clear. The thyroid was small. The trachea was in the midline. The heart sounds were of good quality, no murmurs. The lungs were clear to auscultation and percussion. The liver and spleen were not palpable.

Letter (January 2, 1948): "I can report that I am as well as ever and it is certainly a wonderful feeling."

Case 2. Mrs. R. L. (No. 386001), a 36 year old white woman, a maternal aunt of case 1, entered the Johns Hopkins Hospital on May 19, 1946. Early in childhood a doctor told her of a heart murmur, but she recalled no episode suggestive of acute rheumatic fever. Between the ages of 16 and 18 years she experienced some attacks of palpitation which, together with moderate thyroid enlargement, resulted in a subtotal thyroidectomy. Ten days after the operation, she was seized with a sudden headache, the first of a long series of violent paroxysmal episodes.* A description of a typical attack in order of appearance of symptoms follows: Sudden onset of throbbing headache, sensation of hair standing on end, palpitation, aching in the legs and arms, nausea, and a desire to eructate, profuse sweating over the entire body, and a sensation of pin pricks up and down the spine, with tingling of the tongue. These attacks would usually last about 20 minutes, frequently terminating in a violent sneeze. The patient felt very weak and exhausted for several hours after each attack. Because of continuation and increasing frequency of these episodes, the patient entered a hospital in New York at the age of 27, nine years after their onset. After x-ray studies and perirenal air insufflation, a diagnosis of left adrenal tumor was made. At operation the tumor was found apparently originating in the adrenal and so adherent to the pedicle of the kidney that the tumor with the entire adrenal and

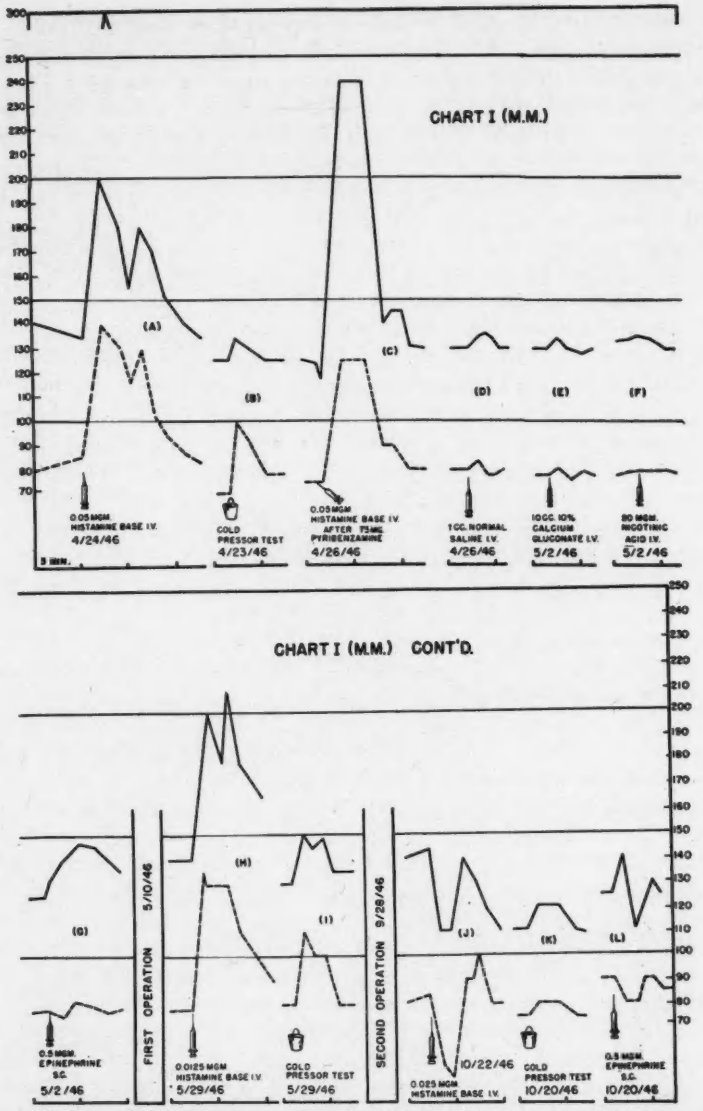

FIG. 6. Case 1. Chart showing preoperative diagnostic measures. Following removal of first tumor, histamine test definitely positive, indicating that active tumor tissue is still present. Following second operation, histamine test negative, indicating that all active tumor tissue has been removed.

the kidney were removed. The diagnostic measures and operation at that hospital admission have been reported in detail by Beer, King and Prinzmetal.

The patient was free of attacks for approximately 9 months after the operation. She had suffered with them ever since with the exception of complete freedom during her first pregnancy 7 years before the present admission. During her second pregnancy 4 years before the present admission, however, the attacks were so severe that at the eighth month labor was induced; and a healthy child was delivered manually. The patient was told at that time that her blood pressure was "over 200, and there was albumin in the urine."

During the year prior to her admission to this hospital the attacks were more frequent and severe. She was also troubled by almost continuous sweating and "wave-like feelings of hot and cold." Her symptoms assumed two distinct patterns, sometimes one merging into the other, but more often occurring separately. In type 1 there were "headache, blanching of the skin, pounding of the heart, goose pimples and a sensation of hair standing on end." Such attacks were quite regularly induced by exertion and lasted only a few minutes. In type 2 she experienced a feeling of weight in the chest, pain in the episternal notch and down the left arm. Attacks of this sort might last throughout an entire day. Menses were quite regular and normal, and there had been no recent change in weight.

Physical examination revealed a hyperkinetic woman who appeared in good health. Nutrition was normal, and there was no abnormal pigmentation. Examination of the optic fundi revealed narrowing of the fundal arteries and slight nicking of the veins at the crossings. There was no papilledema, and no exudates or hemorrhages were seen. The thyroid tissue beneath the scar was normal to palpation, and there were neither eye signs of Graves' disease nor tremor. There was no lymph node enlargement. The lungs were clear. The heart was overactive but not enlarged; sounds were vigorous, and there was present a rough systolic murmur, loudest at the apex, interpreted as of organic, probably rheumatic, origin. The right kidney was enlarged, readily palpable and not tender. The liver was at the costal margin; the spleen was not felt. Reflexes and peripheral pulses were normal. When the patient was examined while symptom free (except for the almost constant sweating), the blood pressure was highly variable, ranging from 120/80 to 250/140. The cardiac rhythm showed frequent curious changes of which the patient was quite unaware, seemingly unrelated to the blood pressure fluctuations. The rate might be found as low as 50 per minute, with abrupt changes to 140 to 150 per minute, and might be either regular or irregular.

During attacks the following observations were made: Skin pallid and drenched, dyspnea with respiratory rate up to 50 per minute, extreme weakness and mental confusion, much like a patient coming out of an anesthetic. The blood pressure was as high as 280/160, but it should be noted that in such spontaneous attacks the blood pressure was always falling by the time the observer reached the patient, and it may well have reached higher levels.

The patient was discharged from the hospital after only 4 days, because her child became ill. She returned on September 30, 1946 with symptoms unchanged

and physical findings identical. On both admissions she ran a slightly elevated evening temperature (100 to 100.4° per rectum) before operation.

The laboratory data and special studies have been completely described by Calkins and Howard, and only positive findings will be recorded here. The phenolsulphonphthalein test showed a definite diminution of 15 per cent in the first 15 minutes and a total of 55 per cent in 2 hours.

On plain x-ray the outline of the right kidney was fairly well seen, slightly larger than normal, slightly lower in position, contour smooth. The outline of the left kidney was not seen.

FIG. 7. Case 2. Intravenous urogram. Pelvis of right kidney well filled, slightly dilated. Calyces are clearly defined, cup shaped and normal, but upper calyx has been displaced caudally. Contour of kidney is not clearly seen, but above it a soft mass is apparently present. There is no function on left side.

The 5 minute intravenous urogram showed good function on the right side; none on the left. The 15 minute film showed the right kidney well filled, moderately dilated, no distortion, filling defect or obstruction at the ureteropelvic juncture. The calyces were a little larger than normal, but retaining normal cupping. The upper calyx seemed pushed in a downward direction. Above the kidney could be seen what might be interpreted as a large, soft tissue mass (fig. 7).

In the cold pressor test the blood pressure rose from 135/90 to 160/105. When 0.05 mg. histamine base was injected in 10 cc saline, an immediate flush occurred, with fall of blood pressure from 140/100 to 95/80. Within a minute

the blood pressure had risen to 300/90. The skin was pale, respirations were 90 and pulse 150 per minute. The patient's symptoms were the same as during a severe spontaneous attack. Bending, lateral flexion and jumping produced no change in symptoms or blood pressure. Strenuous exercise produced a severe attack but not the curious electrocardiographic pattern, as described by Calkins and Howard.

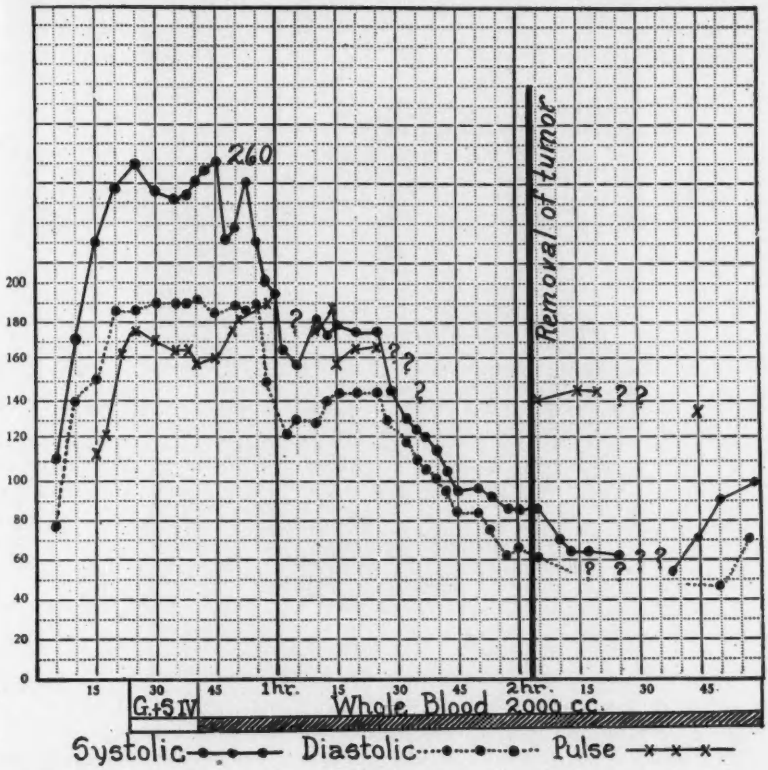

FIG. 8. Case 2. Chart, showing extreme shock when tumor and portion of adrenal gland were removed. Slow recovery from shock by transfusion of whole blood.

From the above findings it seemed evident that an excess of physiologically active chromaffin tissue was still present. As the tumor with the entire left adrenal gland had been removed from the left side, it was decided that the right side should be explored. It must be remembered that the entire adrenal had been removed from the left side so that the operation was undertaken with considerable trepidation, as of course, it was urgently necessary to preserve as much adrenal as possible.

Ether was administered with vinethene induction. The incision was commenced over the tenth rib and continued parallel with the sacrospinalis muscle

and then outward above the anterior-superior spine. The twelfth and eleventh tibs were exposed, stripped of their periosteum and resected close to their articulation. The lumbo-dorsal fascia was opened downward and upward, including the costovertebral ligament. When Gerota's fascia was opened a large but otherwise normal appearing kidney was exposed. Above the kidney could be felt a very large tumor about the size of a grapefruit. This was well encapsulated and gradually separated from the surrounding structures. As in case 1, the adrenal was found spread out over the lower and medial portion of the tumor and intimately attached to the capsule. The upper and medial

FIG. 9. Case 2. Gross specimen. At upper border of tumor on right side can be seen some adrenal tissue, normal in appearance, that was incorporated in capsule of tumor.

portion of the adrenal, however, apparently about one-third, was uninvolved and could be separated from the capsule of the tumor, and was clamped as close to the capsule as possible, divided, and the stump of the adrenal, with the blood supply intact, was preserved. The capsule in the upper portion of the tumor was ruptured, and some tumor tissue extruded. This was wiped out, and the tumor removed by clamping the remaining vascular attachments. Two small tears which occurred in the pleura were closed immediately with medium silk. When the tumor was removed all bleeding had been satisfactorily controlled. The wound was then washed out with alcohol, followed by ether and salt solution.

A rather large tear was then found in the diaphragm which was closed with interrupted mattress and medium silk. The muscles were closed in layers, and a Penrose drain placed down above the kidney. The patient was severely shocked. The pulse at one time was unobtainable, the blood pressure being at times very low. A transfusion and adrenalin were given. The patient was

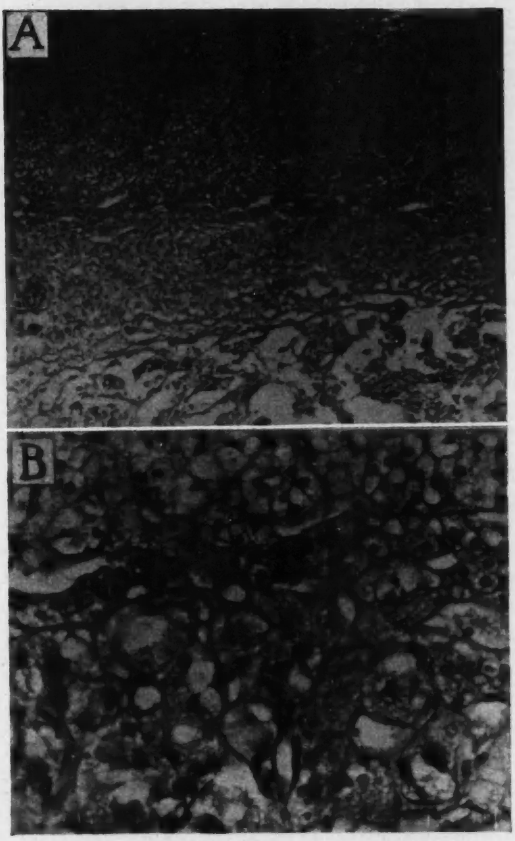

FIG. 10. Case 2. *A*, Low power photomicrograph, showing edge of tumor, and above it, normal adrenal cortical tissue. There is little or no capsule between tumor and adrenal tissue. *B*, High power photomicrograph of tumor tissue, showing same characteristics as noted in case 1.

put in the Trendelenberg position. The pulse steadily improved, and the systolic pressure was 90 when she was taken back to the ward. A considerable amount of blood had been lost (fig. 8).

The postoperative course was stormy, the fever reaching 105 on the second night, and at this time a pneumothorax was evident, which was tapped. The

patient was dyspneic and cyanotic for several days, but after the fourth day her improvement was rapid, and the blood pressure became stabilized. There was some wound infection and phlebitis at the site of the intravenous infusion.

Pathological examination showed the mass (fig. 9) to be a pheochromocytoma surrounded by a thin layer of adrenal cortical tissue (fig. 10). The tumor cells were similar to those in the second tumor removed from M. M., but no tumor cells were found within the blood vessels.

Two weeks after operation there was no clinical or chemical evidence of renal insufficiency. The histamine test was repeated and considered negative (fig. 11).

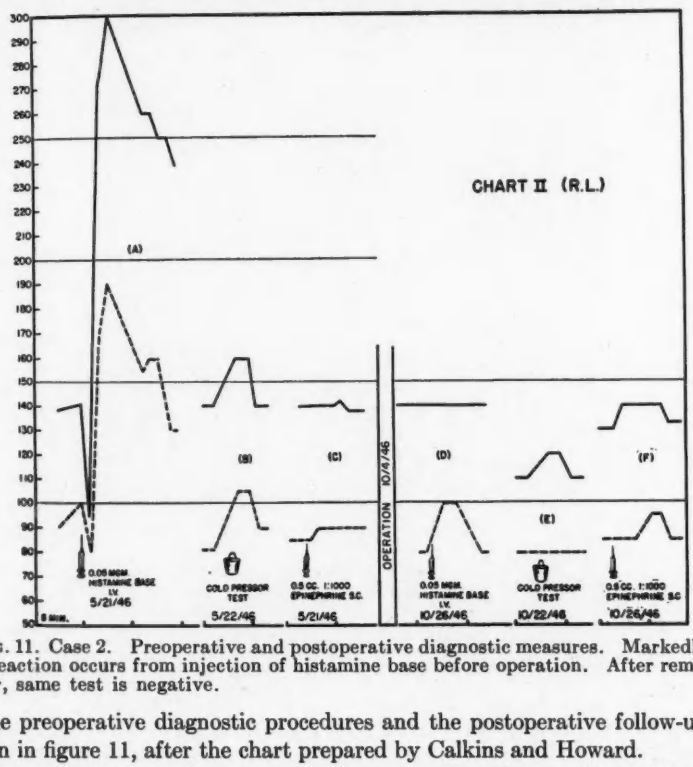

FIG. 11. Case 2. Preoperative and postoperative diagnostic measures. Markedly positive reaction occurs from injection of histamine base before operation. After removal of tumor, same test is negative.

The preoperative diagnostic procedures and the postoperative follow-ups are shown in figure 11, after the chart prepared by Calkins and Howard.

A letter from the patient 4 weeks after operation (February 6, 1947) stated: "Anything resembling previous attacks has completely disappeared. The blood pressure is 120/80. Absolutely no sweating, and I am quite strong. My circulation does not appear to be normal however. My hands blanch from the palms to the fingers, and at times the tip of my nose is usually cold." These symptoms of Reynaud's disease had been present since the age of 18, and had not been materially altered by her first operation.

The patient has recently been through a normal pregnancy, and gave birth

to a normal child. Letter (January 8, 1948): "This pregnancy has been most uneventful. My pressure remains at 115/80 or less. Everything has been very satisfactory."

SUMMARY

Two unusual cases of bilateral pheochromocytomata in blood relations are reported in full. In case 1 a pheochromocytoma had been removed 4 years previously at operation elsewhere, but owing to technical difficulties, it was necessary to leave behind a portion of the capsule. A recurrent tumor apparently developed from this portion of the capsule, and was successfully removed by operation. The hypertensive crises, however, still persisted, with a positive histamine test 4 months later. A second pheochromocytoma was exposed at operation on the opposite side and successfully removed.

The patient's maternal aunt had been operated on elsewhere 9 years previously, and a pheochromocytoma, the entire adrenal and the left kidney removed. She was relieved of symptoms for 9 months, but the hypertensive crises recurred. A diagnosis of pheochromocytoma on the opposite side was made, and at operation a large tumor was exposed and successfully removed.

The diagnostic value of the histamine test has been emphasized.

The technical difficulties at operation are discussed, and the suggestion advanced that the exposure of both adrenal areas might be more satisfactorily carried out through an upper transverse abdominal incision. The advantages of such an approach are obvious, providing sufficient exposure can be obtained to remove a tumor if one should be encountered.

This report is intended in no sense to be a complete follow-up, but case 1 has now been well for 17 months, has had no further hypertensive crises, and the histamine test is negative, so that as of to date it might be safely concluded that no further excess of physiologically active chromaffin tissue is present.

Case 2 reports that she has been well in every respect, and has had no return of hypertensive crises for a period of 16 months. The histamine test has not been repeated in this case, but the patient has recently been through a normal pregnancy with delivery of a normal child, and reports that her blood pressure has never been above 115 systolic and 80 diastolic.

I wish to express my appreciation to Drs. Evan Calkins and John Eager Howard of the Department of Medicine for their courtesy in making available the complete clinical records of these patients.

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A NEW RENAL SYNDROME: MEDIAL PTOSIS OF THE KIDNEY

GEORGE C. PRATHER

Probably on more than one occasion urologists have examined patients for pain or discomfort which because of its character and location was thought to be of renal origin, only to find the pyelographic studies normal. In at least a few of these cases, the symptoms may be due to medial ptosis of the kidney.

Caudal mobility of the kidney with the body in the vertical or upright position (ptosis of the kidney) has been known for many years as a clinical entity, with alternate periods of popularity and disrepute. With that subject we are not directly concerned.

Little or no attention has been given to medial or lateral mobility of the kidney, and the pyelographic demonstration of an abnormal degree of medial mobility has not, to my knowledge, been previously described. Medial ptosis of the kidney has been chosen as a term to describe abnormal medial mobility of that organ. With a patient lying on the left side the condition of medial ptosis of the right kidney would be shown by abnormal change of the position of the right kidney toward or beyond the vertebral column. Similarly medial ptosis of the left kidney might be demonstrated with a patient lying on the right side.

This condition, which may be the cause of symptoms, cannot be demonstrated by the usual pyelographic technique. It can be demonstrated, however, by means of x-ray films using anteroposterior projection with the patient in lateral position (fig. 1). After cystoscopy and ureteral catheterization or during intravenous pyelography the patient is placed on a litter lying on his or her side with the painful side up. The patient's back is placed firmly against an upright x-ray table used for gastro-intestinal or chest x-rays, or against a 14 by 17 inch cassette in front of which has been placed a portable Sieman's micro grid (Adlanco X-ray Corp.). The x-ray tube is then focused for an anteroposterior view of the kidney region. A retrograde pyelogram is then made, with the ureteral catheter pulled down into the lower ureter before the x-ray is taken. A routine film taken in this position during intravenous pyelography may be used instead.

In order to determine the normal extent of medial mobility of the right kidney with the patient lying on the left side, we have obtained films taken in the position shown in figure 1, after completing routine pyelographic studies in a number of patients. As illustrated in figures 2 and 3, these studies show no medial descent of the kidney in the normal individual.

The condition of medial ptosis has been demonstrated and corrected in 2 patients recently. Both were slender females who had moderate pain and distress in the upper right quadrant of the abdomen and right flank. At times the symptoms were noticed or were aggravated when the patient was lying or sleeping on the left side. Physical activity also frequently produced discomfort. Mild gastro-intestinal symptoms appeared to be associated with the pain. There were no urinary symptoms. Both patients had found relief by resting in a supine position. Physical examination in each was normal except that a suspicion of an abnormally movable kidney was created by palpation of the upper abdomen with

the patient lying on her left side, and in 1 of the 2 cases the kidney could be felt in the epigastrium while in a similar position. X-ray studies of the gallbladder, stomach and intestines were reported normal. Intravenous urograms were like-

FIG. 1. Position of patient for pyelogram to demonstrate abnormal medial mobility of right kidney. X-ray taken as anteroposterior projection with patient in lateral position: the painful kidney up.

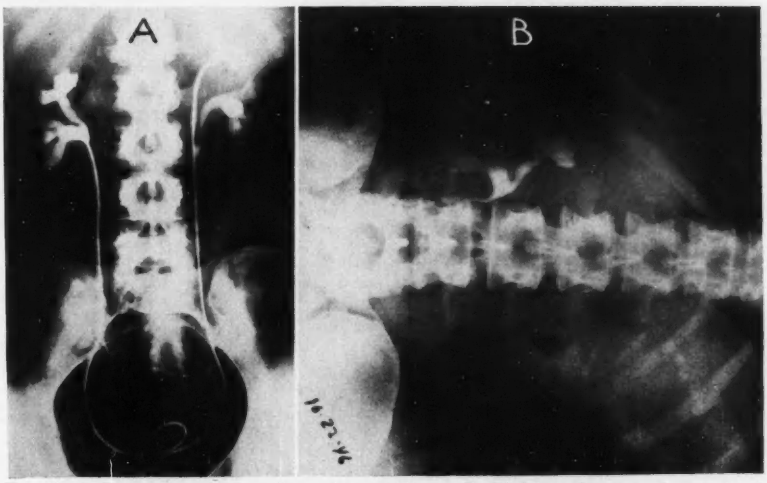

FIG. 2. *A*, Normal pyelogram in supine position. *B*, Right pyelogram of same patient in new position, as shown in figure 1. Kidney remains in normal position.

wise normal. The question of medial ptosis arose, and special studies of the right kidney established the diagnosis.

Figure 4 shows the retrograde pyelograms in supine position in each patient. Figure 5 reveals the extent of caudal mobility with the patients in an upright position. Patient A shows some, but not significant, vertical ptosis, while patient B shows none. From these films it certainly would not be possible to state that the right kidney was the cause of symptoms in either case.

However, by means of films taken in the new position described in this paper

(fig. 6) a significant degree of medial ptosis of the right kidney can be demonstrated in both patients. Patient B appears to have considerable degree of medial mobility.

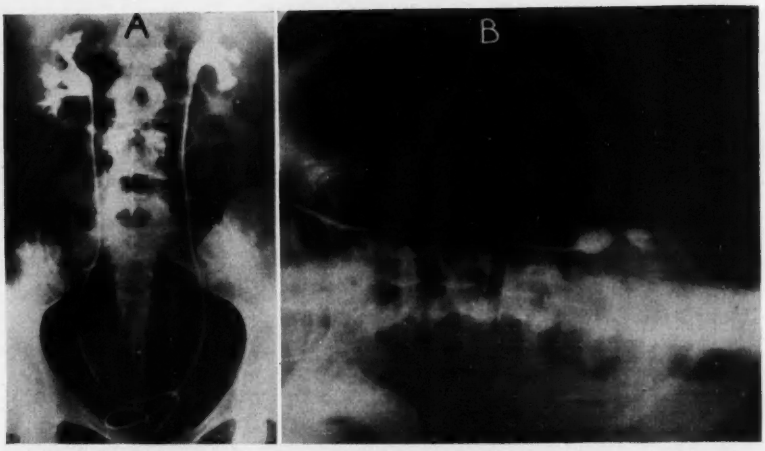

FIG. 3. *A*, Normal pyelogram in supine position. *B*, Right pyelogram of patient in new position shown in figure 1. Kidney remains in normal position. Notice fluid level in kidney.

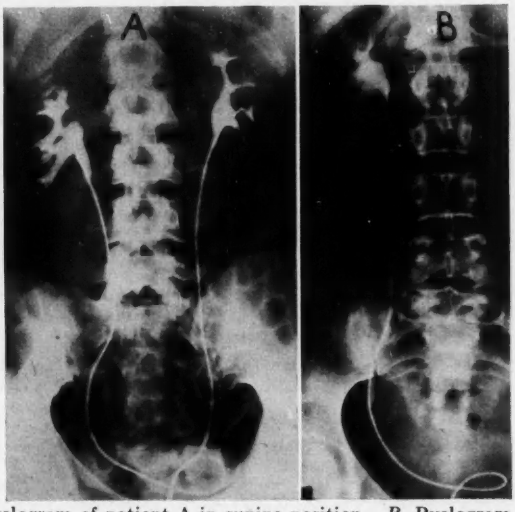

FIG. 4. *A*, Pyelogram of patient A in supine position. *B*, Pyelogram of patient B in supine position.

Nephropexy was performed on both patients with complete relief of symptoms, and postoperative films in the new position (fig. 7) show that medial ptosis has been corrected in each case.

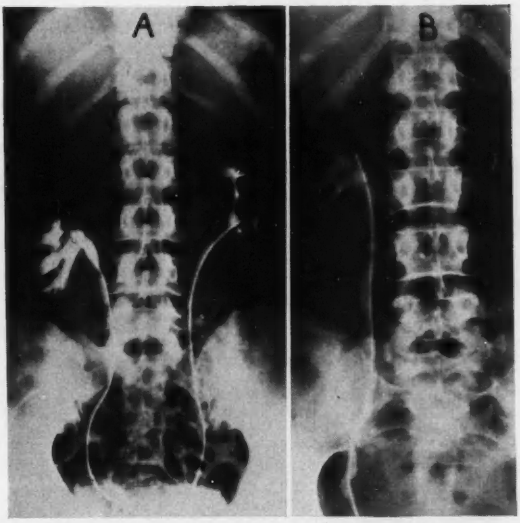

FIG. 5. *A*, Pyelogram of patient A in upright position. *B*, Pyelogram of patient B in upright position.

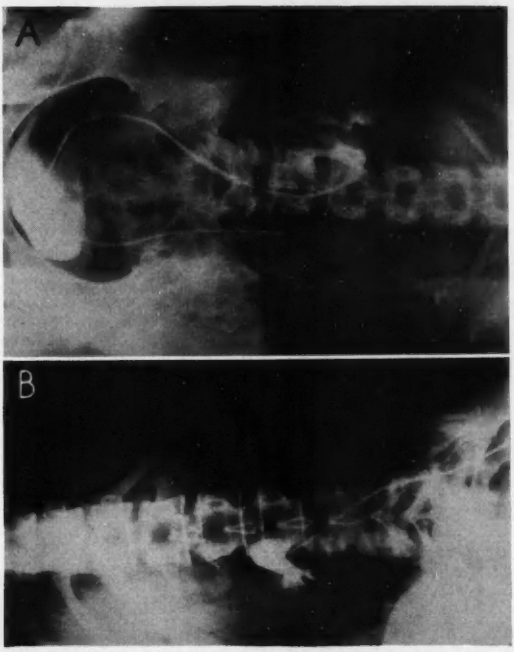

FIG. 6. *A*, Pyelogram of patient A in new position shown in figure 1. There is abnormal medial mobility of kidney in this position. *B*, Pyelogram of patient B in new position shown in figure 1. There is abnormal medial mobility of kidney. It has dropped beyond midline and carried ureter with it.

It is my belief that this syndrome, medial ptosis of the kidney, may explain some of the hitherto undiagnosed symptoms referable to the kidney regions and

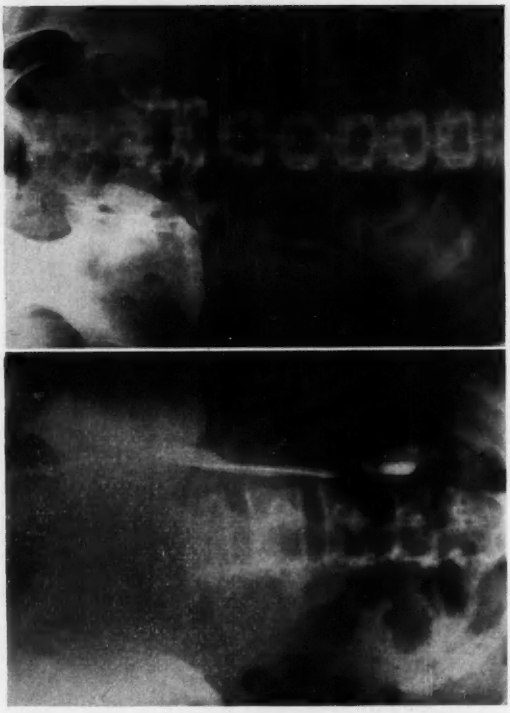

FIG. 7. *A*, Postoperative pyelogram of patient A in new position. Kidney is now in normal position. *B*, Postoperative pyelogram of patient B in new position. Kidney is now in normal position. Notice fluid level in kidney. Foetal spine can be seen.

upper abdominal quadrants. Nephropexy is a simple method of correcting the condition.

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DISCUSSION

DR. CLYDE L. DEMING (New Haven, Conn.): I should like to ask Dr. Prather about the emptying time of those two kidneys where the physiology was entirely normal.

DR. PRATHER: The emptying time was not done, Dr. Deming.

URETERAL ECTOPIA OPENING INTO THE SEMINAL VESICLE[1]

WILLIAM J. ENGEL

From the Cleveland Clinic, Cleveland, Ohio

Cases of ureteral ectopia opening into the seminal vesicle are of interest not only as curiosities but because their reporting stimulates consideration and further recognition of the condition in surgical diagnosis. Riba, Schmidlapp, and Bosworth last year reported a case diagnosed clinically and could find only 4 others which had been recognized during life. Thirty-two autopsy cases were collected. The case to be reported was diagnosed clinically, and further interest is afforded by the fact that the patient sought consultation because of sterility, the circumstances of which are rather unusual.

CASE REPORT

A man, aged 21, consulted me in March 1947, because of sterility. He had been married for 9 months and there had been no conception. His wife had been found to be normal. Of particular interest in his history was the fact that, although he experienced a normal orgasm, at no time had an emission of semen ever been observed either at the time of coitus or with nocturnal dreams. The patient had no urinary complaints.

The clinical history and general physical examination disclosed nothing abnormal. Rectal examination revealed a soft, symmetrical prostate of average size. The left vesicle was rather soft and compressible but was otherwise not remarkable. Massage of the prostate yielded no secretion.

The urinalysis and blood studies were negative.

A preliminary x-ray film of the abdomen was negative. The intravenous urogram showed prompt function from the right kidney. This kidney was large, the kidney pelvis visualized well and was normal (fig. 1, *A*). At no time during the urogram series was any dye visualized on the left side.

Microscopic examination of a post-coital urine specimen revealed 10 to 20 spermatozoa, mostly nonmotile, per high power field.

A McCarthy panendoscope was passed without difficulty. The right ureteral orifice was in the usual position and appeared normal. The left half of the trigone was thrown into rounded, cystic elevations which covered the area normally occupied by the left ureteral orifice and extended out to the vesical neck, producing some encroachment (fig. 1, *B*). Upon withdrawal of the instrument into the prostatic urethra, considerable increased engorgement was noted. The verumontanum was enlarged and edematous, and immediately proximal to the verumontanum and to the left of the midline was an irregular, dark, cavernous opening (fig. 2, *A*). Curiosity led me to explore this with a ureteral catheter, and it was found that the catheter passed out of sight into this cavity (fig. 2, *B*).

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 7, 1947.

Twenty per cent skiodan was injected into the catheter, and the film shown in figure 2, *C* was obtained.

It will be seen that the ureteral catheter became coiled in a large, lobulated cystic dilatation of the seminal vesicle, and from this there emerged a dilated ureter extending up to a hypoplastic kidney lying in normal position.

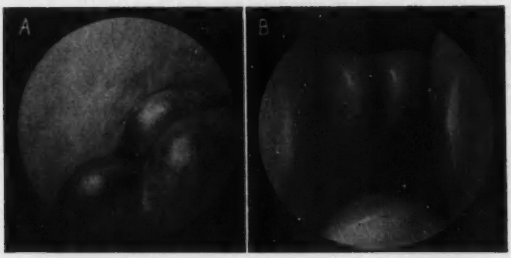

FIG. 1. *A*, Cystoscopic view, showing multilocular cystic elevation in region of bladder normally occupied by left ureteral orifice. *B*, Urethroscopic view of posterior urethra showing cavernous opening on left between verumontanum and vesical neck.

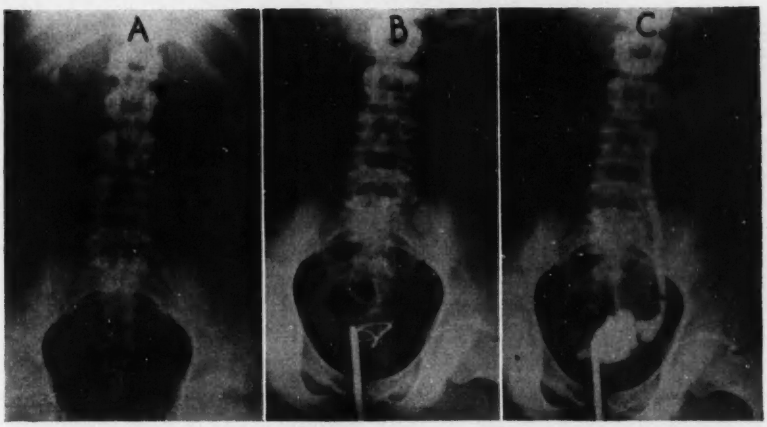

FIG. 2. *A*, Intravenous urogram film, showing absence of function in left kidney. Compensatory enlargement of right kidney. *B*, Showing ureteral catheter coiled in dilated, cystic left seminal vesicle. *C*, Opaque medium injected into catheter, outlining cystic dilatation of seminal vesicle with dilated ureter emptying into it. Kidney is hypoplastic.

The diagnosis was left renal hypoplasia with ureteral ectopia opening into the seminal vesicle, which showed cystic dilatation.

The detailed embryologic explanation of this anomaly has been reviewed in several published articles. In brief, it is due to failure of the normal shifting of the terminal portion of the wolffian ducts and the ureteric bud. When this development is faulty the ureter may remain attached to the lower end of the wolffian duct as the result of which the ureter may open into any organ or structure derived from the terminal portion of this duct. Thus the opening may

occur abnormally in the ductus deferens, seminal vesicle, ejaculatory duct, or the posterior urethra. Thom lists the following incidence of these various locations: prostatic urethra, 33; seminal vesicle, 17; vas deferens, 6; ejaculatory duct, 5.

Associated developmental anomalies are frequently observed, and this patient had a hypoplastic nonfunctioning kidney in addition to the ectopic ureter. In the 20 cases collected by McKirdie and Polkey the kidney was absent in 6, rudimentary in 10, and cystic in 3. Reduplication of the ureter is common, only 1 of the 2 usually being ectopic, however. There is no recorded case of bilateral ectopic opening into the seminal vesicle and no explanation for the recorded preference for the left side. (Of 23 cases tabulated by Hamer et al., 16 were on the left, 7 on the right. McKirdie and Polkey reported 20 cases, 14 on the left, 6 on the right.)

The case here presented has, in addition, a cyst of the seminal vesicle. This is demonstrated radiographically by the multilocular cystic dilatation of the vesicle, and a cystic elevation of the left half of the trigone was seen by cystoscopy. This case, therefore, corresponds to the one reported by Hamer, Mertz and Wishard. Deming has suggested that the most likely explanation for cysts of the seminal vesicle is antecedent stenosis of the ejaculatory duct. In our case the findings suggest that the cyst ruptured into the prostatic urethra, giving rise to the rather large, cavernous opening seen on urethroscopic examination.

Our case differs from the other recognized clinically in that all other reported cases had pyuria, and urinary symptoms were present in all but 1. It will be noted that this patient had no urinary symptoms, and his urine was microscopically negative. His complaint was sterility due to inability to ejaculate. I believe the explanation is that the opening in the posterior urethra permits the semen to reflux into the cavity formed by the cyst of the vesicle and the dilated ureter. This explanation presupposes that the right vesicle and ejaculatory duct are functionally normal, evidence for which is supplied by the finding of sperm in a post-coital urine specimen.

Operation has been advised for this patient. A seminal vesiculectomy and ureteronephrectomy is indicated to correct the anomaly, and it would seem that hope of correcting the sterility lies in closure of the opening in the prostatic urethra.[2]

SUMMARY

A case of ureteral ectopia opening into the left seminal vesicle is presented in which a preoperative clinical diagnosis was made. Only 5 other cases diagnosed clinically have been reported.

In addition to the ureteral anomaly this patient had a hypoplastic kidney and a multilocular cyst of the seminal vesicle.

Sterility due to inability to ejaculate was the complaint which brought the patient for examination. We believe this inability is due to the reflux of semen into the dilated, cystic vesicle.

[2] The patient has since returned for operation and the above findings confirmed. A cystic seminal vesicle was removed and a ureteronephrectomy performed. Convalescence was uneventful but we cannot yet report any effect upon the patient's sterility.

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MEGALO-URETER[1]

EDWARD W. CAMPBELL

"Megalo-ureter" was applied by Caulk in 1923 to designate a congenital dilatation of the ureter. It was his intention, undoubtedly, that the term should apply to a definite congenital, pathological entity. This concept has been forgotten or misconstrued; for, in the literature, it is loosely applied to any enormous ureteral dilatation, whether congenital or acquired.

Caulk, in his paper, referred to Saintu as having first described this type of ureteral dilatation in 1896. Saintu made his first observation from a dissection of a 7½ month fetus. He described the ureters and kidney pelves as enormously dilated, with relaxed, atonic ureteral orifices, without evidence of infravesical obstruction.

Papin and Legueu (1912) in their discussion of congenital hydroureter reported 4 similar cases and listed 3 criteria essential for the diagnosis of this lesion: 1) Great dilatation of both ureteral orifices, which are gaping and show no movement of opening or closing; 2) complete communication between the bladder and renal pelvis; 3) complete filling of the urinary tract when the bladder is filled with an opaque medium, as demonstrated by roentgenogram.

Eisenstaedt (1926) reported 2 similar cases and quoted the requirements of Papin and Legueu. Eisenstaedt called this state of ureteral dilatation, megalo-ureter and referred to Caulk's previous case presentation.

The term megalo-ureter was hereby applied by Caulk and Eisenstaedt to a similar state of ureteral dilatation with two distinct anatomic differences, for Caulk's case report does not satisfy the requirements formulated by Papin and Legueu. Caulk did not mention ureteral reflux and an examination of his pyelogram will reveal a narrow terminal ureter approaching normal, similar to the urogram reproduced in figure 1. Also, Caulk emphasized the presence of a normal renal pelvis in his case report. Both of these points vary distinctly with Saintu's original description.

To further substantiate the confusion of anatomic similarity, most recent attempts to explain the etiology have shifted from the urethra to the ureter. Chwalla (1927) described a vestigial membrane which, by its valvular action, could cause ureteral dilatation. Vermooten championed Chwalla's suggestion in 1939, and referred to a study of 37 urograms to illustrate his contention. Examination of the roentgenograms reproduced in Vermooten's paper showed narrow terminal ureteral spindles similar to Caulk's case. Perry suggested achalasia of the terminal ureter and M. F. Campbell discussed the frequency of ureteral stricture under the title of megalo-ureter. These causes could not possibly be an etiologic factor for the type of anatomic anomaly presented by Saintu, where ureteral reflux is a prime requisite.

The term megalo-ureter heretofore has been used to designate two congenital

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 5, 1947.

states which, although both present great dilatation of the ureter, have two distinct anatomic variations. It seems, therefore, they should be distinguished by a separate title. In a discussion of the etiology I shall refer to Saintu's type of ureteral dilatation as megalo-ureter and to the anomaly which Caulk presented as congenital hydro-ureter.

ETIOLOGY

Although the literature on megalo-ureter is rather sparse, considerable research has been conducted relative to its etiology, from which theories of its

FIG. 1.—Pyelogram made with No. 10 occluding catheter. Tip of catheter is seen at base of dilated ureter and metal bulb is in intramural ureter, a spindle of normal calibre. Note angle of junction between dilated and narrow ureter.

causes rather than factual evidence have been evolved. The theories may be divided into three groups.

1. *Obstruction.* An infravesical obstruction of some type would seem the most likely cause, but the absence of any visible evidence of obstruction has been emphasized in all case reports of megalo-ureter. Urethral valves or membranes have been suggested to exist in fetal life, which disappear at birth. MacMyn has described the presence of occult folds in the posterior urethra which act as obstructive valves. He claims these can be discovered by careful dissection of the urethra. The occurrence of unilateral megalo-ureter, as reported by Hilliard, would argue against infravesical obstruction as a cause for this type of anomaly.

2. *Neurogenic dysfunction.* A disturbed or deficient nervous mechanism

has been suggested by Thompson in his discussion of Couvelaire's paper. This would be similar to the state produced by a cord lesion, which is usually bilateral and accompanied by a large bladder. This does not correspond to megalo-ureter, especially when unilateral.

In this respect megalo-ureter has been likened to a megalocolon, the etiology of which is not proven. I have found no reference to sympathectomy for the relief of megalo-ureter, which, if it were effective would strengthen this supposition.

3. *Arrested development.* Muscle fibers appear first at the third month of fetal life. They arise next to the bladder and extend upward to involve the entire ureter and pelvis at about the middle of the fourth month. Gerard and Loraine, from their studies of the development of the fetal ureter, have demonstrated the presence of enormously dilated ureters up to the fourth and fifth month of fetal life. This finding was so constant that Loraine has suggested it as the "norm" for the first stage of embryonal life.

This period of ureteral dilatation corresponds to the time required for full muscular development of the ureteral wall. Some factor which might cause the arrestment of muscular development could well perpetuate the dilated ureter. This to me, would seem a more logical conception of the etiology than Gerard's theory, that from this state of dilatation, the organ, instead of diminishing in calibre, continues to develop concurrently with the rest of the body and remains voluminous in size during adult as well as fetal life.

These are the theories for the etiology of megalo-ureter, only one of which, neurogenic dysfunction, could possibly be a cause for congenital hydroureter. No peristalsis of the dilated ureter was noted on intravenous urography in the 5 cases reported in this paper. Four of these ureters which were operated upon showed no ureteral contractions following artificial stimulation, but this is not unique, for the same occurs in acquired hydroureter. Muscular atrophy of the ureter, which might well be expected from deficient innervation, was not evident in any sections of the ureteral wall studied in our group of patients. This is especially noted (fig. 2, *A*) in the oldest patient in this group (age 50 years) by which time atrophy should be apparent if it were going to appear.

The excellent development of the muscular coat of the ureter in all our specimens readily eliminates arrested muscular development as a possible cause. On the contrary, the muscular layer was well developed, almost to the point of hypertrophy. This is demonstrated in a section of tissue (fig. 2, *B*) removed from the ureter of a patient 23 years of age, which might represent the mid-point of development in age range of our group of patients.

Normal muscular development in the later age group with evidence of diminished renal function suggests continued work, although peristalsis is not evident. Hypertrophy in the middle age specimen with better renal function suggests compensatory development to counterbalance some obstructive phenomenon. The more normal muscular coat in the older patients may represent a stage of recession from continued overwork and diminished renal function. Fibrous tissue replacement was more evident in the specimens from the two older patients. This may, in part, be the result of prolonged infection.

Obstruction, therefore, appears to be the most possible cause for congenital hydroureter. This is my reason for the change of terminology. Dilatation of the renal pelvis, the result of a congenital obstruction at the ureteropelvic junction, is termed congenital hydronephrosis. Transplantation of an obstructive

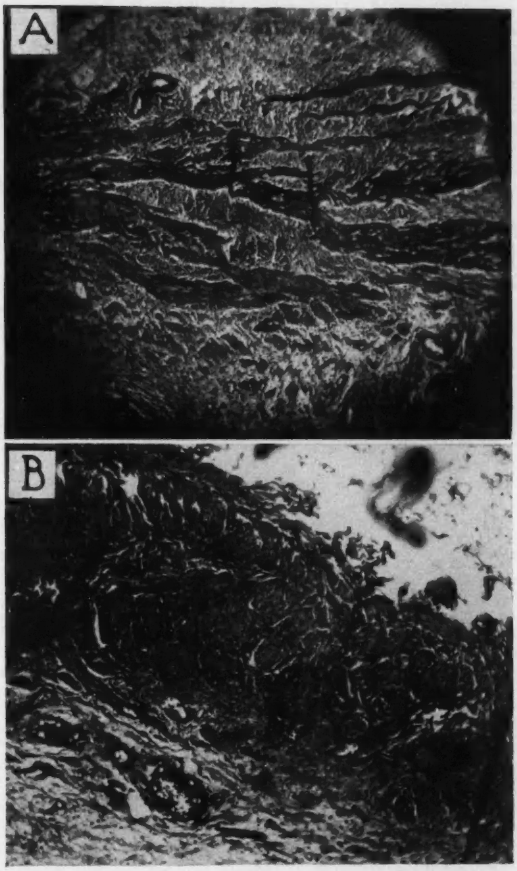

FIG. 2. *A*, Tissue section from lower, dilated portion of ureter of 50 year old patient. Same case as figure 1. Muscular coat is well developed with little evidence of fibrous replacement. *B*, Section of tissue removed from right ureter of a 23 year old patient. Same case as figure 7. Wall was thickened due to a well developed muscular layer.

lesion from the upper to the lower ureter would, therefore, suggest the term hydro-ureter, thus reserving the term megalo-ureter for non-obstructive dilatation.

What the obstruction is in congenital hydro-ureter is neither constant nor always discernible. Bottomley has demonstrated valvular elements in the lower ureter. Chwalla demonstrated a possible cause for the development of

such valves. Vermooten suggested their presence from urographic evidence; such proof is open to question and could be accepted only with histologic proof. One would expect obstruction of this type to cause dilatation from a lower level rather than the higher level evidenced in all our patients. A diligent search was made for the presence of valves in 4 patients who were operated upon, but none were found. In one of our patients the ureteral orifice would not admit a No. 4 bougie, meatotomy permitted dilatation to No. 10 without symptomatic or anatomic benefit.

FIG. 3. Intravenous urogram made after numerous ureteral dilatations on left side, showing no recession of ureteral dilatation which might be expected with relief of obstruction and infection.

Strictures as demonstrated by Eisendrath were not present in our patients, for catheters of varying sizes were readily introduced from below upward, and above downward in all operated cases. Relief from dilatation of a possible fibrous stricture of large calibre was beneficial to one patient, due more to relief of infection than the dilatation, for there was no regression of the size of the ureter following dilatation (fig. 3).

The terminal segment of the ureter was removed for study from 2 patients. Neither showed any obstructive factor. From the youngest of this group, aged 7, sections of tissue are reproduced in figure 4. The first, *A*, was taken from the narrow terminal segment. This shows string-like portions of longitudinal fibers which continue down to the intramural portion of the ureter. Immediately above this area, where the ureteral lumen abruptly dilated a sec-

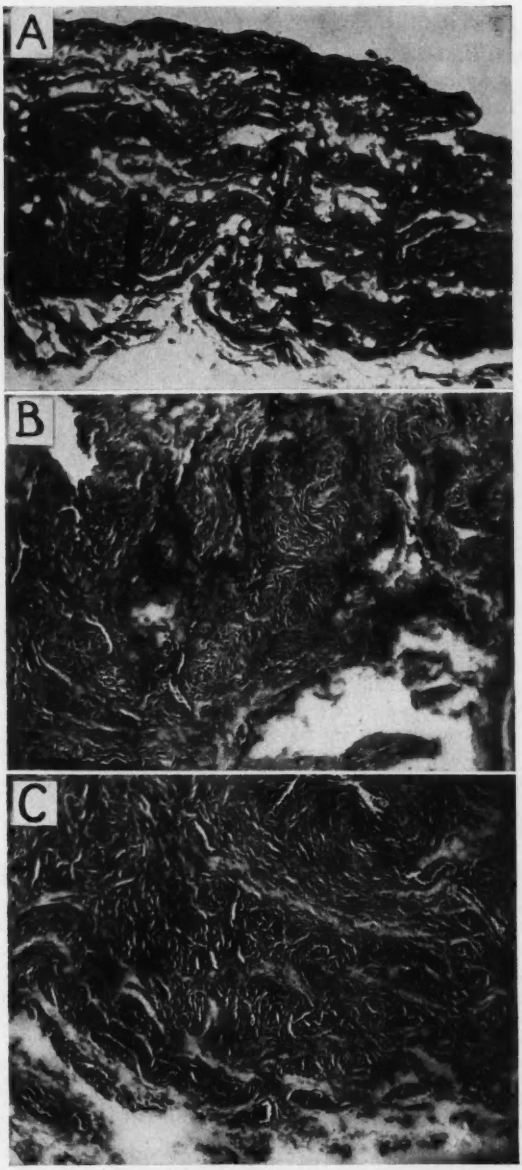

FIG. 4. Sections were made from three portions of terminal segment of the left ureter of a 7 year old boy. Same case as figure 6. *A*, Section of wall from narrow spindle showing normal longitudinal musculature. *B*, Section of tissue from ureteral wall at junction of dilated and narrow spindle. Muscular coat is slightly thicker than normal, but not hypertrophied. No evidence of a fibrous stricture. *C*, Muscular coat is wider in this section of dilated ureter which suggests hypertrophy of muscular wall, the result of an obstruction.

tion of tissue, *B*, shows a comparatively normal muscular layer. There was a thought, at first, that the muscular wall might be thickened at this point to produce a constricting ring. Further study did not prove this point. As a matter of fact, sections from the distended ureteral wall in juxtaposition to the narrow segment tend to show an hypertrophy of the muscular coat, *C*. There is no evidence of fibrosis at the site of constriction, but obstruction is again emphasized by the hypertrophy of the ureteral wall immediately above the apparently normal ureteral segment.

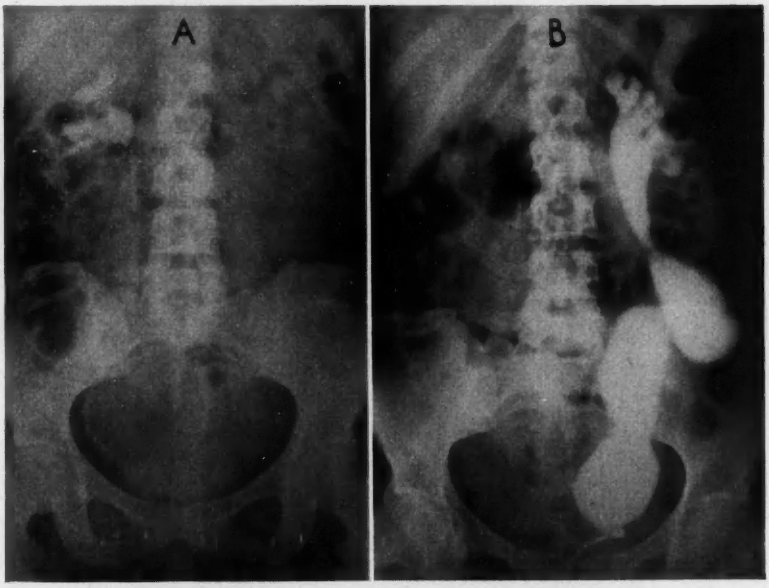

FIG. 5. Case 4. *B*, Pyelogram, showing minor renal dilatation in comparison with enormous ureteral dilatation, a point stressed by Caulk. Note angle of junction of dilated ureter with terminal normal segment. On left an intravenous urogram reveals a normal right urinary tract.

It is interesting to observe the angle of junction between the distended ureter and narrow ureteral segment in the pyelograms. The catheter passes through the intramural ureter in an almost horizontal plane to enter the larger ureter at an obtuse angle, instead of a gentle curve (figs. 1 and 5). This characteristic was as prominent in the youngest as well as the oldest patient (fig. 6). Careful dissections of the juxtavesical ureters were made on 3 occasions to visualize the ureter as it entered the bladder wall. In all 3 instances the dilated ureter extended below the level of the ureteral entrance and seemed to pull the narrow segment of ureter downward to produce the angle demonstrated on the roentgenogram. This phenomenon in itself can exist as an obstructive factor. It seems to me it is more than likely the result of prolonged backpressure, with dilatation and subsequent lengthening of the ureter, rather than the initial

cause of congenital hydroureter which begins, for some unknown reason, during fetal life.

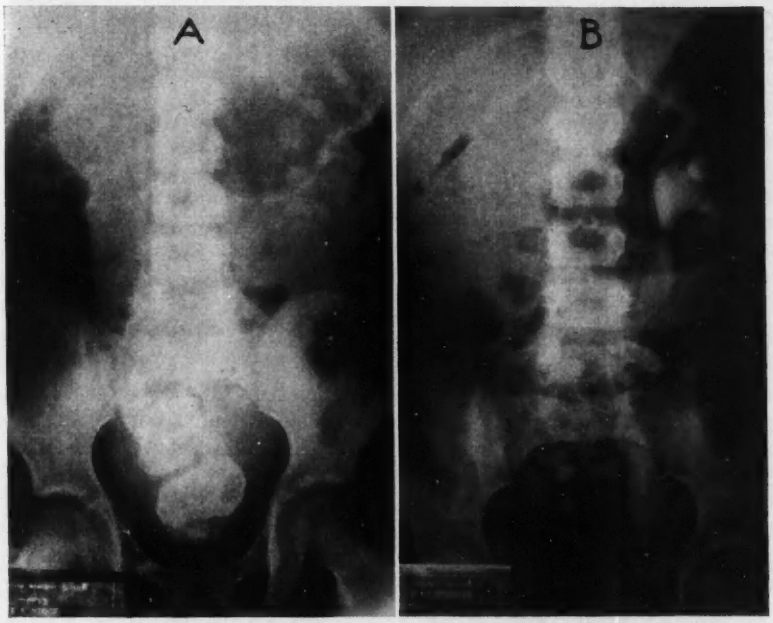

FIG. 6. Case 1. Intravenous urogram of a 7 year old boy. Five minute film on left shows normal right renal pelvis and ureter. Thirty minute film reveals dilated left ureter. Sections of terminal portion of left ureter are shown in figure 4. Left ureter at time of an attack of pain became so large it could be palpated through abdomen.

CASE REPORTS

Case 1. W. M., a white boy aged 7 years, was admitted to the hospital September 7, 1946, with a chief complaint of abdominal pain. He had had recurrent bouts of pain about the umbilicus for 3 years. More recently the distress had become more frequent and was associated with vomiting and an elevated temperature. One month before admission to the hospital a tender mass was noted in the lower left abdomen by the family physician, who referred him to another hospital and an appendectomy was performed. For 3 days prior to admission to our hospital the boy had been mildly febrile.

The patient was admitted to the general surgical service where the only positive finding was a mildly tender mass in the lower left abdomen. Gastrointestinal series and barium enemas were made. September 17, 1946, an intravenous urogram (fig. 6) showed a normal right urinary tract. On the left side there was a greatly dilated ureter with only a mildly dilated renal pelvis. There was an abrupt obstruction at the lower portion of the ureter immediately beneath which was a thread-like column of dye as the ureter entered the bladder. The bladder outline was normal and there was no apparent increase in size.

General physical examination was negative except for some enlargement of the cervical lymph nodes. These were firm, not tender, and movable. Abdominal examination revealed a vague, soft, smooth, slightly tender mass in the lower left quadrant. There was no costovertebral tenderness and no palpable enlargement of either kidney. Peristalsis was hyperactive and there was no ridigity.

Laboratory studies: Hemoglobin 10.7 gm.; red blood cells 3,700,000; white blood cells 6,600; polynuclear cells 76 per cent; lymphocytes 20 per cent; monocytes 3 per cent; eosinophiles 1 per cent. Blood urea nitrogen 16 mg. per cent; blood chlorides 582 mg. per cent; Co2 combining power 37 volumes per cent; sugar 58 mg. per cent. Urinalysis negative chemically and microscopically with a specific gravity of 1.022.

Cystoscopic examination (September 20, 1946) revealed a normal bladder mucosa. There were no trabeculations of the bladder wall, the outlet was negative and no obstruction at the outlet could be noted. The ureteral orifices were closed and not inflamed. A urine spurt could be seen on the right side, but no active peristalsis was seen on the left side. A No. 5 catheter was inserted through the left ureter for a distance of 20 cm., without obstruction. The urine obtained from the left renal pelvis was slightly hazy due to pus cells. A culture of the urine showed Staphylococcus albus.

On September 23, 1946, through a low left paramedian incision, the peritoneum was exposed and then dissected medially down to the level of the external iliac vessel where a large, tortuous, tubular mass was identified to be the ureter. Dissection was carried down to the bladder where the ureter was found to become abruptly smaller, approaching the size of a normal ureter. This portion was dissected down to the bladder wall and was doubly clamped and cut. It was this lower portion of the ureter including a small part of the dilated ureter which was removed for study, the sections of which are reproduced in figure 4. After straightening the ureter as much as possible, a portion was resected and the remaining stump was transplanted into the bladder over a No. 14 whistle catheter as a splint. A mushroom catheter was inserted into the bladder through a stab wound for suprapubic drainage.

The boy had an uneventful convalesence until the ureteral catheter was removed, 48 hours following which his temperature became elevated with the occurrence of the left loin pain. An intravenous urogram showed greater dilatation of the kidney pelvis and ureter than previous to transplantation, with poor drainage through the site of anastomosis. The anastomosis had apparently held well, but the opening into the bladder was too small to permit adequate drainage with a resulting pyonephrosis.

October 25, 1946, it was necessary to do a nephrectomy on the left side.

Pathologic report: The diameter of the dilated ureter was 1.4 cm. in contrast to 4 mm. in the narrow portion, while the lumen at the ureteropelvic junction was 6 mm. No valves were demonstrated in the ureter. Microscopic examination of the upper ureter showed the mucosa to be normal, the submucosal tissues

showed fairly marked infiltration of small, round cells, occasional polymorphonuclears and an occasional eosiniphile. There was a moderate degree of edema and proliferation of fibroblasts. There was slight thickening of the ureteral wall due to an overgrowth of connective tissue and some hypertrophy of the musculature. In some portions of the ureter there were areas of connective tissues replacement in the muscle wall.

Case 2. M. S., a white female 22 years of age, was admitted to the hospital May 1, 1939, with the complaint of abdominal pain and swelling on the left side. Her family history revealed no history of similar anomalies. During her childhood she had had many diseases common to that period. At 4 years of age an appendectomy had been performed and some glands were removed, the details of which were not known. The patient was well until 7 days before admission when she was taken with a severe pain in the left side, which pain did not radiate and lasted for only 24 hours. Seven days later the pain recurred and at that time a swelling was noted in the left side. The swelling was tender, the pain was sharp, but did not radiate. There was no nausea or vomiting and no disturbance of bowel habits. There were no urinary symptoms of frequency, dysuria, or hematuria. Menses were regular.

On examination the patient was found to be much smaller than the average girl of her age due to extensive developmental bone changes. These caused marked physical deformities. General physical examination was negative. Blood pressure was 120/70. Abdominal examination revealed a large mass extending from the crest of the ilium to the left costal margin and medially almost to the umbilicus. The mass was soft and very tender, especially at the flank. There was no movement of the mass with respiration.

Laboratory studies: Hemoglobin 13.5 gm.; red blood cells 4,300,000; white blood cells 13,200; polynuclears 38 per cent; lymphocytes 17 per cent; monocytes 4 per cent; eosinophiles 1 per cent. The Wassermann and Kahn tests were negative. Blood urea nitrogen 12 mg. per cent; blood sugar 76 mg. per cent; blood chlorides 564 mg. per cent; combining power 49 volumes per cent. Blood calcium 9.8 mg. per cent; blood phosphorus 5.2 mg. per cent, which was later checked and found to be 3.6 mg. per cent on 2 occasions. Blood cholestrol 216 milligrams per cent. Urinalysis on admission was cloudy, acid, specific gravity 1.025, 8 to 11 white blood cells per high power field and no red blood cells. Temperature, pulse, and respirations were normal.

May 2, 1939, an intravenous urogram (fig. 7, *A*) showed a nonfunctioning kidney on the left side. On the right side there was a greatly dilated ureter with only mild dilatation of the pelvis and calyces. The ureter terminated in a narrow segment of ureter of normal calibre. There appeared to be no filling defect from a calculus or other pathologic change as an obstructive cause for the dilatation.

May 8, 1939, cystoscopy was done. The urine was slightly hazy. The bladder mucosa covering the fundus of the bladder was normal, there was no excessive enlargement of the bladder cavity, no trabeculation. The inflammatory changes were confined entirely to the trigone and the base of the bladder

surrounding this area. The trigone was markedly edematous with edema extending up to and surrounding the left ureter for a distance of 2.5 cm. The drainage from this catheter was thick and yellow due to pus. One hundred and thirty cubic centimeters of urine were drained from the left ureter and pelvis. The right ureter was not catheterized at that time.

A pyelogram (fig. 7, *B*) revealed an enormously dilated and tortuous left ureter. No stone could be observed as an obstructive factor. In view of the bilateral dilatation a diagnosis of megalo-ureter was made. Studies were made

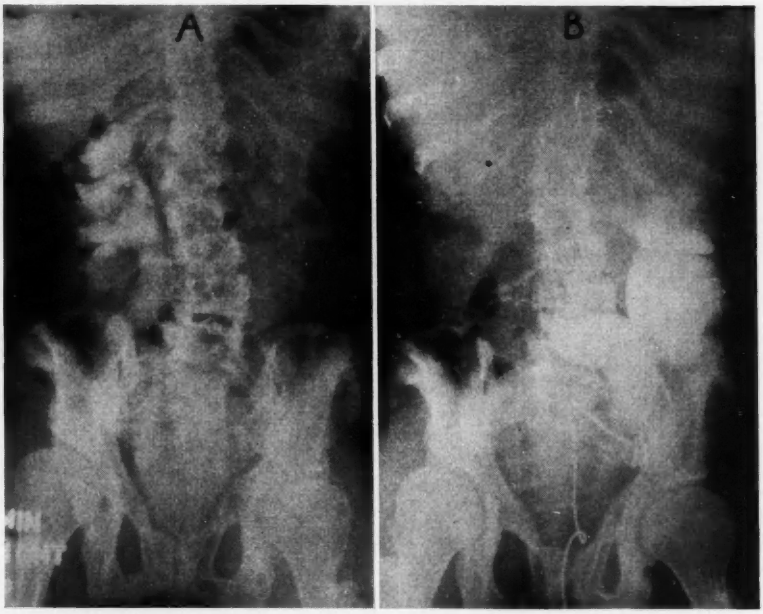

FIG. 7. Case 2. *A*, Intravenous urogram, showing dilated right ureter and nonfunctioning left kidney. Section of tissue was removed from right ureter and is reproduced in figure 2, *B*. *B*, showing enormously dilated left ureter.

for the tubercle bacillus, all of which smears were negative. These were negative on two subsequent occasions.

Following cystoscopy the patient's temperature was elevated and catheter drainage was continued for several days, following which her temperature remained normal after the removal of the catheter. The patient returned at frequent intervals for ureteral dilatation for 18 months, at the end of which time it became impossible to pass ureteral catheters. The patient had a marked febrile reaction and a nephrostomy was performed because of the state of the opposite kidney. Nephrostomy drainage has been carried on continuously since 1941, to the present time without evidence of return of function on the left side.

Pyelograms have been made through the nephrostomy drain and it has been repeatedly shown that the ureter has not diminished in size, even with the relief of backpressure.

In the early part of 1947, the patient had vague pains on the right side and was admitted in February 1947, because of right renal colic. At that time a stone was found in the lower portion of the ureter which was too large to pass. An ureterotomy was performed, and a small section of tissue was removed from the ureter for study (fig. 7, *A*).

It is interesting that the ureterotomy wound healed promptly and has remained healed, which would not be expected in the presence of a marked obstruction. At the time of operation a No. 6 catheter was passed into the bladder from above to demonstrate the absence of obstruction.

Case 3. A. F., a white woman aged 34 years, was admitted to the hospital February 16, 1929, with a chief complaint of hematuria. Past history was negative except for backache 5 years previously. There had been occasional mild attacks of dysuria with nocturia. She stated that at times she had noticed pus in her urine. This was not substantiated by urinalysis. Hematuria appeared for the first time 3 days before admission to the hospital and was not accompanied with abdominal pain or backache. There was no dysuria or frequency.

General physical examination was negative. Abdominal examination showed no abdominal tenderness or rigidity. There was no costovertebral tenderness and, although both kidneys could be palpated, they did not feel enlarged. Vaginal examination was negative. Blood pressure 122/80.

Laboratory studies: Hemoglobin 85 per cent; red blood cells 4,700,000; white blood cells 7,000; polynuclears 70 per cent; lymphocytes 26 per cent, monocytes 4 per cent; blood urea nitrogen 12 mg. per cent; blood Wassermann was negative.

Cystoscopic examination revealed a bladder of good capacity and normal tone; the mucous membrane of the fundus was normal. There was some mild hyperemia about the base of the bladder and trigone. The ureteral orifices were negative. The left ureteral orifice was rather tight to the passage of a No. 6 catheter, but a No. 5 catheter was inserted with ease. Bloody urine was found to be coming from the left side. There was a large amount of retained urine, the quantity was not estimated. The urine from that side was bloody and had a very offensive odor. Colon bacilli were cultured from that side. The right ureter was catheterized with ease. The urine was negative for evidence of infection.

An intravenous urogram showed a greatly dilated ureter on both sides which terminated in a normal sized ureter passing through the bladder wall. Both kidney pelves were slightly dilated and there was only mild caliectasis. A diagnosis was then made of bilateral megalo-ureter.

Because of the diffculty to pass a No. 6 catheter, a ureteral meatotomy was performed on the left side, following which ureteral dilatation was carried out periodically until a No. 11 Garceau catheter could be inserted. Ureteral dilatations and irrigations were continued until 1930, when the patient was asymptomatic and only a few pus cells remained in the urine.

April 1931, the patient returned with marked hematuria from the left kidney. At that time colon bacilli were again cultured from the urine. A phenolsulphonphthalein test showed 24 per cent output in a 30 minute period from the left side and 30 per cent from the right kidney. Further ureteral dilatations and irrigations were continued until the patient was asymptomatic.

The patient was last seen June 1937, at which time she complained of frequency and burning on urination, but had had no hematuria. Sulfanilamide was given because of a colon bacillus infection in the left upper urinary tract. This rapidly relieved her symptoms and reduced the infection.

An intravenous urogram showed no regression of the ureteral distention as the result of ureteral dilatation which had been continued over a long period of time (fig. 3).

Case 4. Mrs. J. L., a white woman aged 44 years, was admitted September 12, 1944, with the chief complaint of pain in the back on the left side and burning on urination. The family history was unimportant. She had had rheumatism at the age of 5 and 15 years. The gallbladder and appendix and a fibroid uterus were removed in 1935. She had a nervous breakdown in 1938. She had had an indefinite backache for a period of 5 or 6 years. A diagnosis had been made of gallbladder disease for which she had been receiving gallbladder drainage. X-rays of the gallbladder, however, were negative. For the past 6 to 8 months she had had distress in her lower left side which had become more intense and more frequent. With this distress she had burning on urination, but only a mild degree of frequency, no urgency, no hematuria. Nocturia 2 to 3 times. Bowel function normal.

General physical examination was negative, except for abdominal examination which revealed tenderness in the gallbladder area. No costovertebral tenderness was present on the right side. The lower right abdomen was also negative for masses or tenderness. On the left side, there was definite costovertebral tenderness with muscle spasm. Examination of the lower left abdomen revealed a sense of firmness, but no definite mass, some muscle spasm and rigidity.

Laboratory studies: Urine acid, specific gravity 1.004, albumin 3+ plus, 5 to 10 red blood cells, and 15 pus cells per high power field. Hemoglobin 11.2 mg., red blood cells 4,800,000; white blood cells 6,200; polynuclears 77 per cent; lymphocytes 23 per cent. The Wassermann and Kahn tests were negative. The blood urea nitrogen was 12 mg. per cent.

Intravenous urogram September 12, 1944, showed prompt excretion of the dye in the 5 minute picture. On the right side there was a normal urinary tract except for nephroptosis. On the left side in the 30 minute picture some dye appeared in the terminal calyces which were globular in shape, suggesting a marked hydronephrosis.

Cystoscopy September 16, 1944, revealed a normal bladder mucosa, no evidence of enlargement of the size of the bladder, no trabeculation. The right ureteral orifice was normal; the urine was negative microscopically and on culture. The left ureteral orifice was so small that it was difficult to insert even a small bougie. A meatotomy was performed and a No. 10 bougie could be readily inserted. Ureteral dilatations were continued for a month, at the end of which

time the patient was experiencing even more pain than she had at the time of her initial admission, and with this considerable infection, with occasional bouts of colic and temperature elevation.

The patient was re-admitted to the hospital October 6, 1944, and on October 9, 1944 a nephro-ureterectomy was performed. A narrow terminal portion of the ureter was identified as in the other cases and immediate examination and section of this portion revealed no evidence of valves even with the use of a hand lens. There was no apparent stricture and it was noted that even though there had been an obstruction at the ureteral meatus still there was no dilatation at the intramural portion of the ureter and there was a segment of ureter above the bladder which was of normal calibre.

Examination of the ureteral specimen revealed the lumen of the dilated portion to be 1 cm. The wall was thickened up to 5 mm. There was some subepithelial infiltration with mononuclear cells suggesting a chronic inflammatory change. The tissue immediately beneath this was somewhat fibrosed with some edema. The muscular wall was slightly thicker than normal, suggesting a mild degree of hypertrophy.

Case 5. M. K., a white female aged 50 years, was admitted to the hospital December 2, 1943, with a chief complaint of pain and burning on urination with pyuria. Past history was negative for contributary illnesses or injuries. For 3 or 4 years before admission to the hospital the patient had experienced periods of burning and pain on urination, at which time pus had been noted in her urine. She had been treated for cystitis, but no urologic examination had been made. For 1 year prior to admission she had had some backache on the right side which had become more bothersome, and was referred for a thorough urologic examination because of intractable infection.

An intravenous urogram before admission to the hospital showed a slight degree of function on the right side with some filling of the calyces in the late picture, but insufficient function to fill the pelvis or outline the ureter. The left ureter and kidney pelvis were normal.

December 3, 1943, cystoscopy revealed a negative bladder. The ureteral orifices were not inflamed; peristalsis was seen on the left but not on the right side. A No. 6 catheter was inserted through the right ureter for a distance of 25 cm. without the slightest obstruction. The urine from this side was cloudy due to a large number of pus cells. Culture showed non-hemolytic streptococci. There was marked hydronephrosis and hydroureter on the right side. At the time of pyelography injection of 160 cc Skiodan caused the patient no distress. The pyelo-ureterogram (fig. 1) showed an enormous dilatation of the entire ureter with moderate dilatation of the pelvis and calyces. There was a narrowing of the ureter in the juxtavesical portion where it approached the normal calibre as it passed through the vesical wall. A diagnosis was made of megalo-ureter.

The patient was re-admitted to the hospital January 11, 1944, at which time a nephro-ureterectomy was performed on the right side. The characteristic narrow terminal segment of ureter was found in the juxtavesical portion. The

ureter was greatly dilated, tortuous, but there were no marked inflammatory changes about the ureter with constricting bands which might have caused obstruction.

Examination of the ampula-like piece with a segment of ureter of normal calibre revealed no evidence of obstructing valves. A section of the tissue at this segment showed no increased fibrosis. The ureter immediately above the point of constriction showed hypertrophied muscular wall with some edema.

CONCLUSIONS

Evidence has been given to prove the existence of two distinctly different types of congenital ureteral dilatation which are now termed megalo-ureter. It is suggested that the term "megalo-ureter" should be reserved solely for enormous congenital ureteral dilatations with atonic ureteral orifices and dilated renal pelves, the type originally described by Saintu.

Huge congenital dilatations of the ureter with a normal terminal spindle should be called congenital hydro-ureter, because obstruction is the most probable cause.

Although no obstructive factor was demonstrated in the 5 cases presented, contributory evidence, namely, hypertrophy of the muscular coat of the ureter, has been given to further suggest the probable cause is an obstructive uropathy.

Attention is called to the angle of junction between the dilated and terminal spindle. This is thought to be a result of ureteral elongation from continued backpressure rather than the initial cause of dilatation.

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A PERSISTENT CLOACA IN A FIVE YEAR OLD BOY[1]

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J. R. A., a male aged 5 years, was admitted to the Pediatric Medical Department of Cook County Hospital on June 20, 1946. His mother had brought him to the hospital because he voided all urine by way of the bowels and she was worried about the small size of his penis.

The child was born at home. The attending physician had informed the mother of the very small penis and of urination by way of the anus. The mother was told that the boy could be operated upon at puberty to correct all of his abnormalities.

This child had what was thought to be attacks of pneumonia when he was 24 and 26 months old. The first attack lasted 2 days and the second attack lasted 3 days. These episodes could have been attacks of pyelonephritis. An examination and a chest film, about 6 months later, disclosed "heart trouble." The mother had noted a rapid pulse and that the boy became tired very easily. There had never been any dyspnea, orthopnea, cyanosis or ankle edema.

This boy had received intramuscular injections of pituitary substance twice a week for 4 weeks, when he was 3 years old, to help enlarge his penis. These injections seemed to make the patient irritable and nervous. A survey indicated a cardiac disturbance and the injections were stopped. There was no change in the size of the penis.

There was no history of congenital anomalies in any other member of the family.

The child was of small stature, pale and shy. His weight was 34 pounds. The blood pressure was 98 mm. of Hg systolic and 70 mm. of Hg diastolic. He did not appear ill.

The facial expression was that of a boy. The 4 front teeth were represented by pegs. The tonsils were enlarged and inflamed. The lungs showed no abnormal changes.

The apical heart beat was very noticeable and diffuse. It was most noticeable at the base of the sternum but was also seen at the left of the midclavicular line. The heart border was enlarged to the left. There was a loud, blowing, systolic murmur throughout the heart field and a slight diastolic murmur.

There was a dimpling in the sacral region above the anus and a small irritated area of the skin just below this dimple.

The rectal examination, with a gloved finger, disclosed nothing of significance. The patient had one to two bowel movements a day. All bowel movements were liquid.

The penis was very rudimentary and appeared more like a clitoris than a penis (fig. 1). The testes were of normal size and consistence for a boy 5 years old.

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 5, 1947.

The scrotum appeared normal except for a groove which extended down the center of the scrotum almost to the anus. The mother stated that a small amount of mucus would appear on the end of the rudimentary penis 2 to 3 times a year. There was no visible external urethral meatus or palpable urethra.

The Wassermann and Kahn tests of the blood were negative for syphilis. Red and white blood cell counts and hemoglobin determination were all within normal limits.

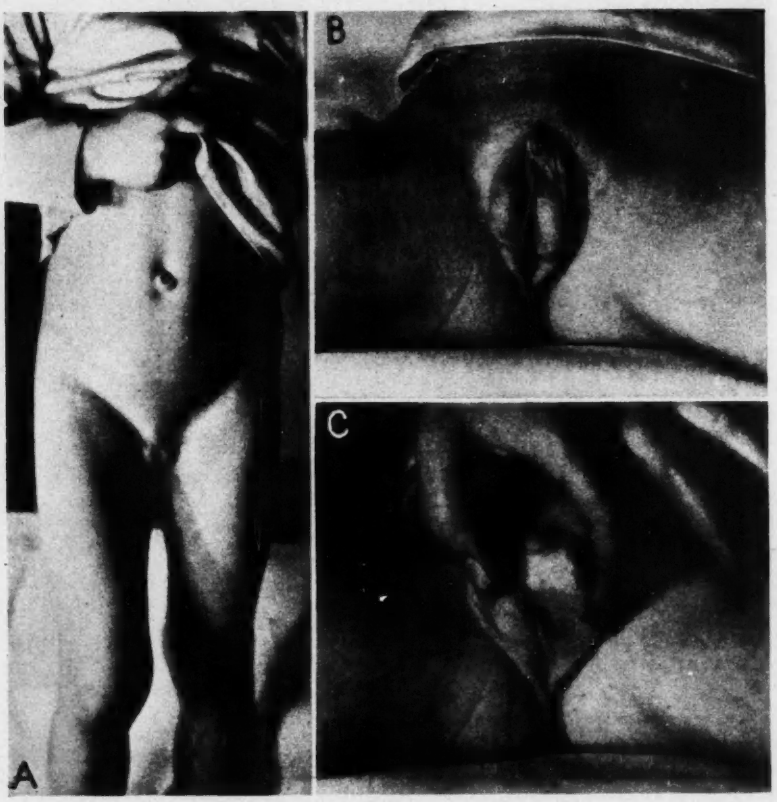

FIG. 1

X-ray study of the chest revealed the cardio-thoracic ratio to be markedly increased. The heart had an abnormal contour in that the left heart border was straight. The vascular markings were increased and radiated in all directions from both hila. The costo-phrenic angles and infraclavicular areas were clear. These findings were compatible with organic heart disease and pulmonary congestion.

The electrocardiographic tracings were definitely abnormal. The auricular

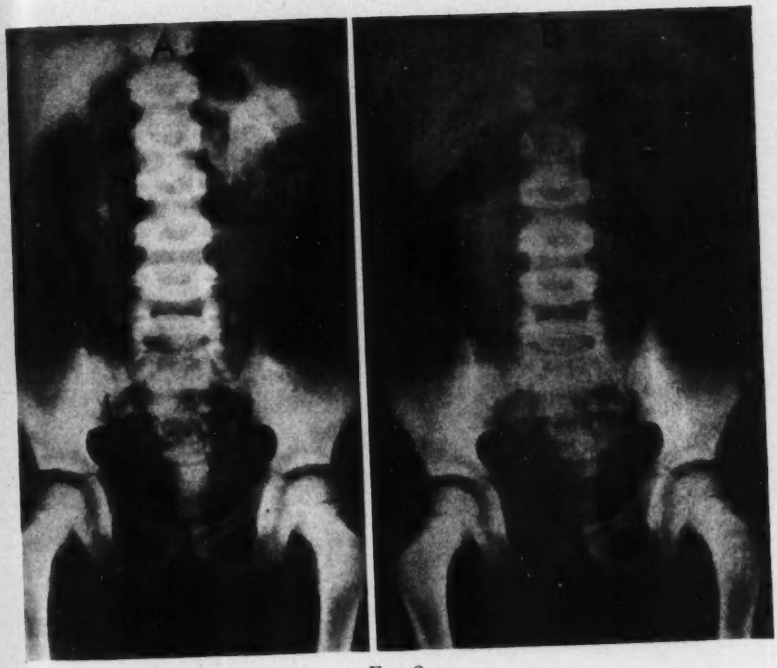

FIG. 2

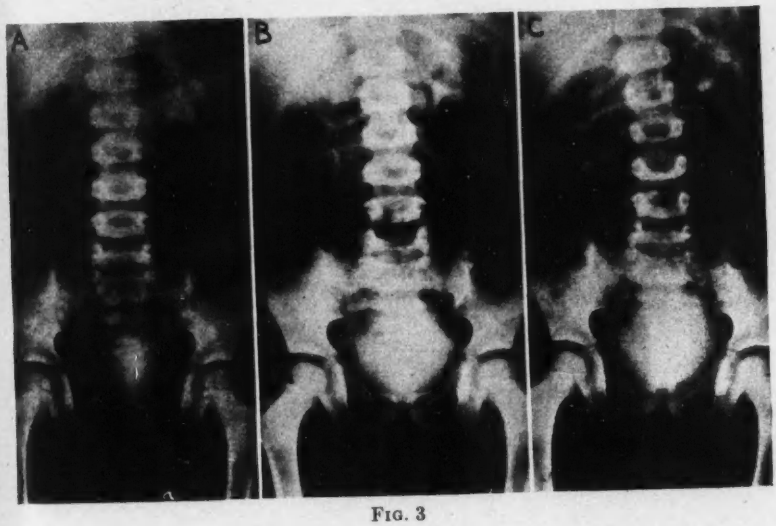

FIG. 3

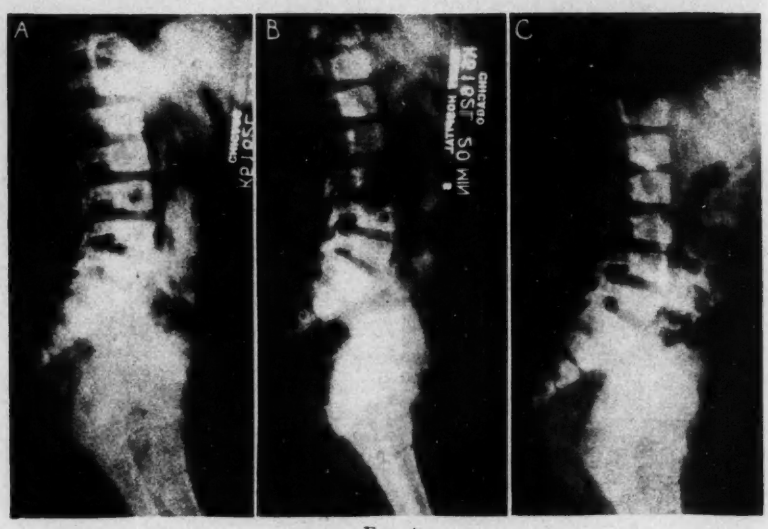

FIG. 4

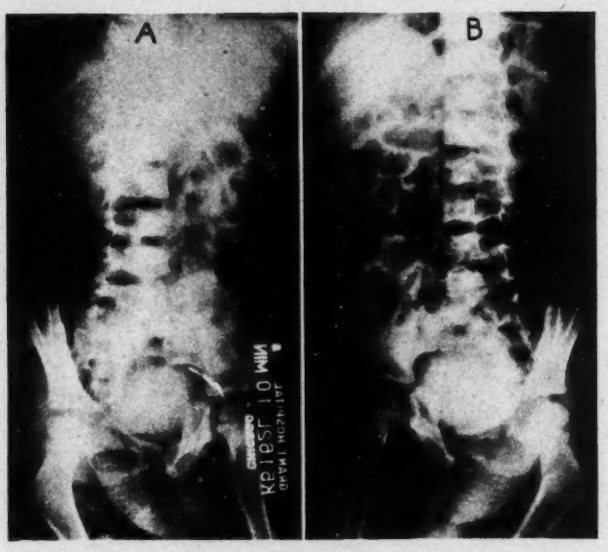

FIG. 5

rate was 96. The tracing showed a sinus rhythm. The P-R interval was 0.12. The Q-R-S interval was 0.06. The Q-R-S was diphasic in Leads I and II and down in Lead III. A deep S_1 and S_2 were present. T_1 was small. P_3 was in-

verted. T_4 was upright This curve is sometimes seen with congenital heart lesions. Repeated electrocardiographic tracings revealed the above changes

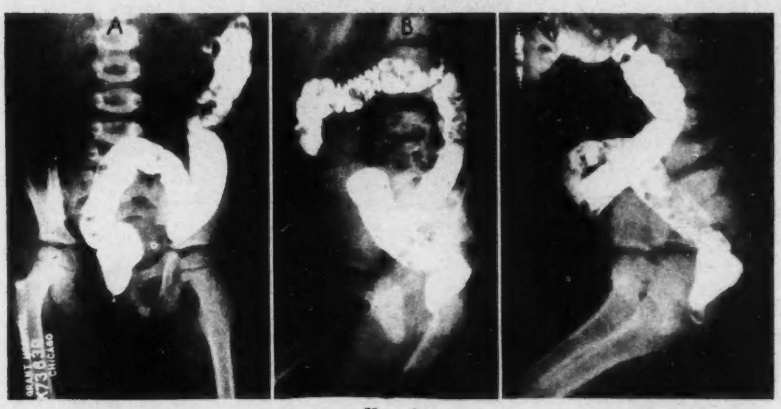

FIG. 6

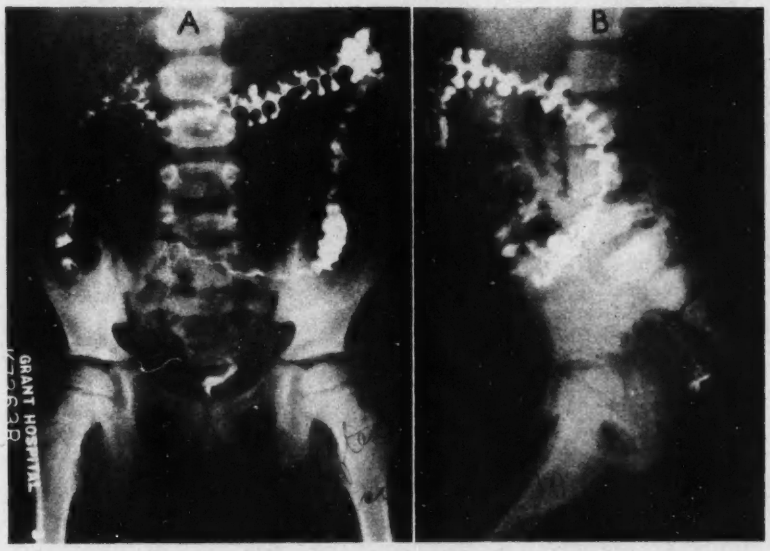

FIG. 7

with right axis deviation. There was also T_1 inversion to suggest myocardial involvement.

Plain x-ray study of the urinary tract showed renal shadows which seemed to be normal in size, shape and position. There was a pelvic shadow which could be interpreted as a full urinary bladder (fig. 2, *A*). Intravenous urograms suggested normal bilateral kidney function on the five minute film. The bladder

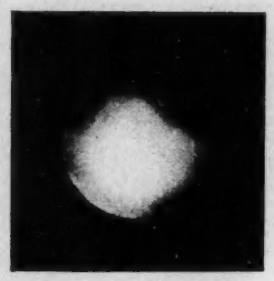

FIG. 8

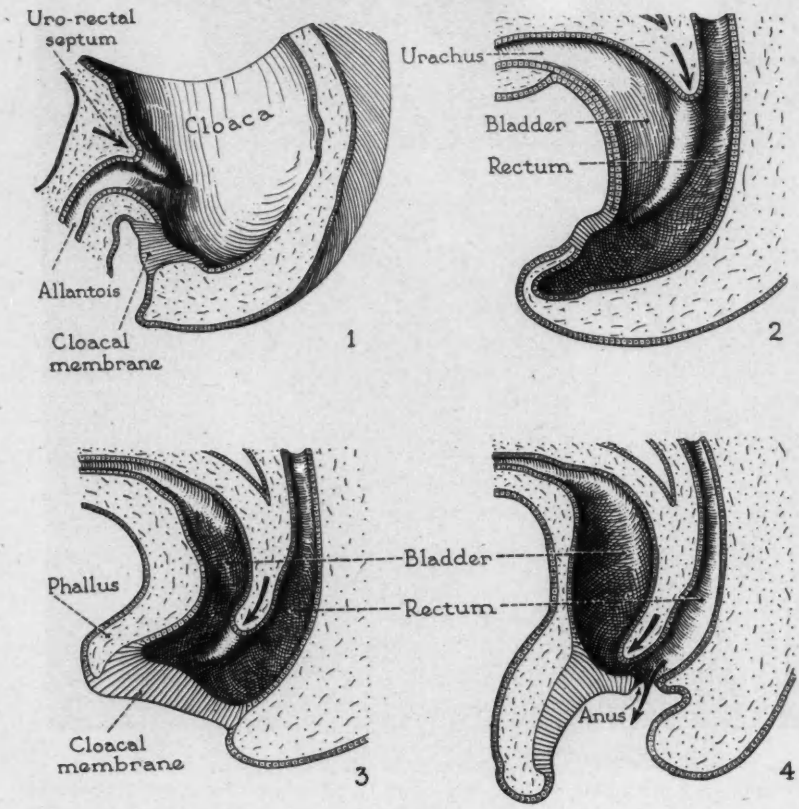

FIG. 9

was seen to be filled with dye. Attention is directed to the double density in the mid-portion of the bladder on each film (fig. 2, *B*). This double density could represent dye outside of the bladder and possibly in the rectum. These findings were very evident in the 10, 20 and 40 minute films (fig. 3). The 10, 20 and 40

minute lateral views revealed nothing of importance (fig. 4). The 10 and 40 minute oblique exposures were not significant (fig. 5).

A barium enema revealed a normal recto-sigmoid area in the anteroposterior, oblique and lateral views (fig. 6). There were no unusual traces of barium in the anteroposterior and lateral views of the rectosigmoid area after evacuation (fig. 7).

A proctoscopic examination revealed a rosette of mucosa on the ventral wall of the rectum just inside the anal sphincter. This was interpreted as a stoma or connection between the bladder and the rectum. It was decided not to pass a catheter through this rosette. Such a procedure would possibly infect the urinary tract. Figure 8 shows a picture of this area which was taken through a proctoscope.

EMBRYOLOGY

Figure 9, *1* shows the dilated caudal segment of the bowel, the cloaca; the allantois empties into this structure. Figure 9, *1* also shows the cloacal membrane which is a thin wall of ectoderm and entoderm. In a 6 week embryo, the urorectal septum, a frontal fold, passes downward to meet the cloacal membrane and separates the cloaca into a dorsal rectal and a ventral urogenital segment, from the dorsal surface of which the ureter stalks and wolffian ducts leave. The upper portion of this anterior or ventral segment becomes the bladder; the inferior portion becomes the posterior urethra in the male and the entire urethra in the female. See figure 9, *2* and *3*. It is believed that in our patient, the urorectal septum never completely joined the cloacal membrane, thereby establishing a connection between the bladder and the rectum. Thus, a persistent cloaca is present (fig. 9, *4*).

We have no evidence of a urethra in this boy. The urethra is usually derived from 1) the lower narrowed portion of the vesico-urethral anlagen above the wolffian duct opening which forms the urethra down to and including the verumontanum and utricle and 2) the urogenital sinus which begins at the openings of the wolffian and müllerian ducts and extends to the cloacal or urogenital membrane which separates the sinus from the cloacal fossa outside.

The ureters, as shown in the foregoing urograms, apparently empty into the usual location of the bladder.

LITERATURE

A search of the literature does not reveal any instance exactly similar to this patient. Campbell reports the autopsy findings in a 3 year old girl whose bladder was exstrophic and who had a rectovaginal fistula. The right ureter opened directly into the rectum and the left ureter ended blindly in the tissues on the side of the bladder. Campbell also reports that he operated on a 6 weeks old male whose right ureter was an impervious cord; there was anal atresia, urethrorectal fistula, a dilated rectum, a left pyonephrosis and a dilated left ureter which opened into the lower rectum.

Walker reports the autopsy on a 12 day old female in whom there was persistence of the cloaca. He termed the condition "ectopia of the cloaca".

Burns describes the autopsy of a 4 hour old infant with exstrophy of the urinary bladder and a persistent cloaca.

Kilfoy operated on a new born child to correct an imperforate anus and found the distal sigmoid greatly dilated, and it communicated with the urinary bladder through a hard fibrous duct. A colostomy was done and the child died 4 days later.

Major reported the autopsy findings of a 1 hour old male who had an imperforate anus and no urethra; there was a wide cloaca into which the rectum and both ureters emptied.

Pennock and Stark operated on 2 male children, 5 years and 18 months old, because they passed fecal matter through the urethra after imperforate ani had been opened at birth. In both instances there was a defect in the floor of the bulbous urethra, which defect was closed successfully in both patients by surgery.

Lowsley has reported successful operations on two girls who had a cloaca.

Wharton has emphasized congenital malformations associated with agenesis of the ovarian follicular epithelium.

We wish to express our thanks to Dr. Leslie B. Arey of the Department of Anatomy of Northwestern Medical School and his artist, Miss Lucille Cassell, for their anatomical and embryological ideas and drawings.

SUMMARY

An instance of persistent cloaca and absence of the urethra in a 5 year old boy is reported. There is also evidence of a congenital heart lesion.

Since this child enjoys good health in spite of the persistent cloaca and since it is doubtful whether surgery would improve that which nature has already done, it was decided not to use any operative interference in an effort to correct his defects. It was also recognized that he would never procreate.

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FAILURE OF THE UROGENITAL UNION[1]

LOUIS M. ORR AND (by invitation) JOSEPH C. HAYWARD AND A. FRED TURNER, JR.

EMBRYOLOGY

Failure of the urogenital union is one of the rarest anomalies of the urogenital system. To consider the developmental events which lead up to that state where failure of the union might occur is to trace superficially the chronology of embryonic life to that phase where initial sexual differentiation of the genital systems takes place.

Anatomists and embryologists have always regarded the reproductive and urinary organs, despite their difference in function, as being one and the same system. This is possibly true for in early embryonic life both empty into the cloaca. By a division of the cloaca into the digestive system and the urogenital system, the two become permanently separated and it is at the point of this division that the anlage for the urethra, the urinary bladder and urogential sinus make their appearance.

Another finding which substantiates the above belief is that the mesonephros, functioning as a primary urinary organ, sacrifices this initial function by uniting with the reproductive system and thus becomes permanently the male efferent duct.

Felix divides the development of the urogenital apparatus into four phases: 1) The development of the urinary glands and their ducts, 2) the development of the reproductive organs and their ducts, 3) the urogenital union: that is, the union between the reproductive and urinary glands, and 4) the development of the urogenital sinus and associated external genitalia.

THE UROGENITAL UNION

Before sexual differentiation takes place, the efferent apparatus for the sexual products of the male is produced in both male and female sexes by union between the mesonephros and the testis. In the degeneration of the mesonephros as a urinary organ, the remaining segments are divided into an upper group, the epigenitalis, and a lower group, the paragenitalis (fig. 1). The epigenitalis, consisting of 5 to 12 tubules and corresponding in relative position to the 58th to the 69th mesonephric tubules, degenerate completely up to the collecting tubules. The point of transition from the secretory to the collecting tubules in the mesonephros is such that the collecting tubules come to lie nearest the surface of the reproductive gland. The blind ends of these collecting tubules become enclosed by the nucleus of epithelium of the reproductive gland so that each tubule end is almost completely surrounded by the nucleus. In that this nucleus gives rise to the rete blastema, it follows that the collecting tubules of what was a part of the the urinary system lie membrane to membrane against the rete tubules of the reproductive organs. The union of these two systems, the urogenital union,

[1] Read at annual meeting. American Association of Genito-Urinary Surgeons. Absecon, N. J., June 7, 1947.

takes place by a disintegration of the membranes at the end of the apposing tubules with a resulting establishment of a single tubule between the mesonephros and reproductive organ (fig. 2). Felix observed this union for the first

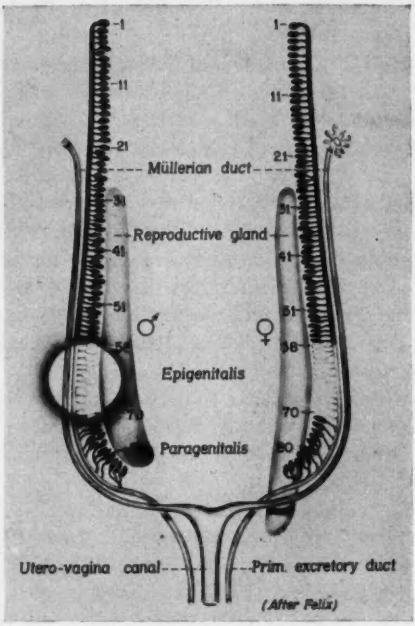

FIG. 1. Diagram of entire renal organ, reproductive gland and efferent ducts. (After Felix, Human Embryology: Keibel and Mall.)

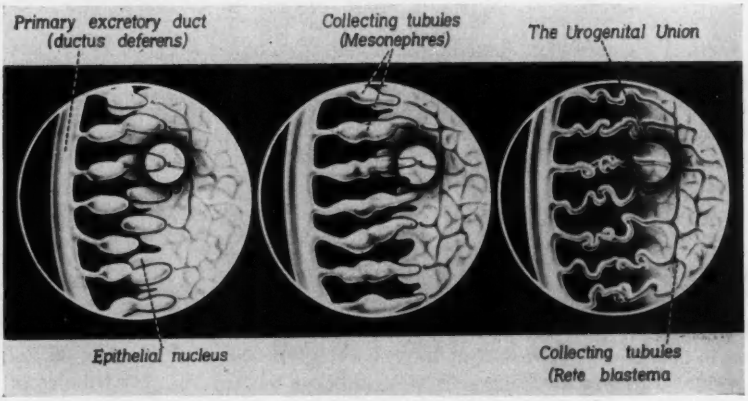

FIG. 2. Diagrammatic conception in development of urogenital union

time in embryos of 60 mm. head-foot length. Up to this time the development in the two sexes is alike. A further development now begins in the males, degeneration in the females.

Failure of the urogenital union is when junction fails to take place between the gonad and the mesonephros; thus, the epididymis and testicle develop separately.

As soon as union between the tubules of the mesonephros and the rete tubules has taken place, they become known as the efferent ducts of the testis and the development of the structure of the epididymis begins. In the fourth to fifth fetal month they develop coils in the direction of the primary excretory duct, the ductus deferens, whereas they remain straight toward the testis. As a result of this arrangement, they give the appearance of triangular shaped objects

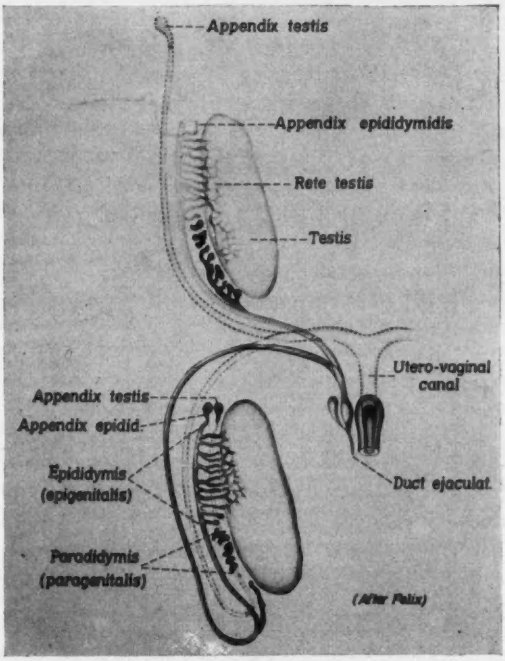

FIG. 3. Development of epididymis before and after descensus of testis. (After Felix, Human Embryology: Keibel and Mall.)

with the apices toward the testis and the bases toward the excretory duct. Later they become surrounded by connective tissue and assume the designation of coni vasculosi. Some of the coni join together to form a longitudinal connecting duct before opening into the testis; thus, a longitudinal canal between the coni and efferent ducts to the testis is developed. All of the tubules of the epididymis or epigenitalis are not involved in the urogenital union. The uppermost tubule becomes the appendix of the epididymis (fig. 3). Other uninvolved tubules which remain are known as appendices retis. The paragenitalis, which plays no part in the union, is divided into several parts and from several of its tubules is developed the organ of Giraldes. Some of the tubules of the paradidymis empty into the medial limb of the primary excretory duct which later becomes the ductus deferens.

CASE REPORT

W. S. B., a 46 year old white male, was first seen on April 25, 1946, complaining of a "misplaced left testicle." Since early childhood there had always been an absence of the left testicle in the scrotum, but a tender mass had been present in the left groin which on numerous occasions had caused pain. The patient ventured the theory that the testicle failed to come down because of an infection in the left inguinal region during infancy as a result of being stuck with a safety pin in that region. Several months prior to his first visit, the mass in the left

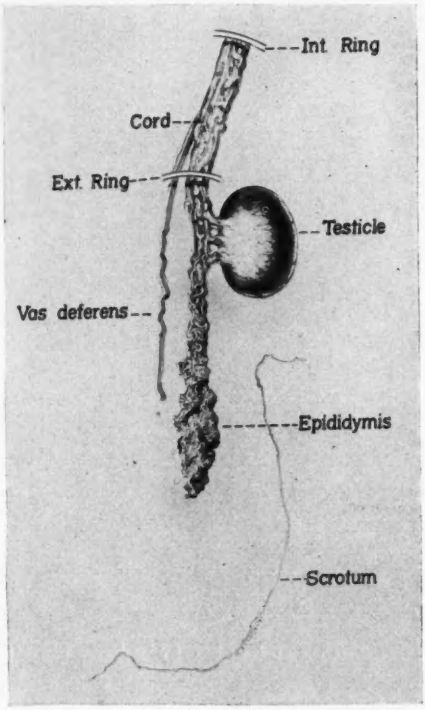

FIG. 4. Failure of urogenital union with blind ending of ductus deferens

groin seemed to descend to the border of the symphysis where it became painful. It had remained in that position up to the present. The patient's general health was excellent. A right inguinal hernia was repaired in 1941 with good results.

The patient was well developed. In the right inguinal region was a well healed right herniorrhaphy scar with no evidence of recurrence of hernia. The right testicle was felt to be smaller and much less firm than normal. The left testicle was absent from the scrotum, but could be palpated just distal to the external ring, being tender and movable, although it could not be displaced

downward. In the standing position, upon coughing, a moderate size left indirect incomplete inguinal hernia was observed with considerable dilatation of the external inguinal ring. In the supine position, the hernia reduced spontaneously and the testicle was easily displaced into the abdomen. There was no evidence of other gross pathological changes on physical examination.

On May 10, 1946 a left orchidopexy and herniorrhaphy was performed. A left inguinal incision through the skin and subcutaneous tissues down to the fascia of the external oblique disclosed a moderately atrophic testicle lying just outside and lateral to the external inguinal ring and attached loosely to the cord (fig. 4). The epididymis and vas were not attached to the testicle, and further dissection and exploration revealed the vas to end blindly at the upper border of the scrotum. The epididymis was noted to be completely separate from the vas and was lying free, slightly distal and also in the upper portion of the left side of the scrotum and attached to the remnants of the cord by blood vessels and nerves. The decision was made to preserve the left testicle in view of partial atrophy of the right testicle which had developed secondary to the previous herniorrhaphy. The testicle and cord were mobilized and freed up through the internal ring and on the posterior lateral peritoneum by dissection of numerous small fibrous bands which permitted sufficient lengthening of the cord to allow transplantation of the testicle to its normal position in the scrotum. The Torek technique was used in maintaining position of the testicle. The hernia was repaired and the wound closed in the usual manner.

LITERATURE

A review of the available literature has revealed but few references to failure of the union between the epididymis and the testis. In no instance was there reported a failure of union of the epididymis and vas deferns and the testis. Windholz (1926) mentions a case revealing complete separation of the epididymis and the testis. Kaufman (1922) reported a similar case.

Brunzema (1929) found this condition on four occasions on operations for undescended testis.

Wilson (1939) records one instance in which the testis was in the inguinal canal with the epididymis in the scrotum.

Ombredanne (1923) mentions that the separation occurs on those occasions when there is a vestigial testis, and Wangensteen (1932) reports a case of an epididymis with a vestigial structure attached to it but which had none of the appearances of the testicle.

Counseller and Walker (1933) quote Polya who, in 1902, described an embryonic variation at the site of attachment of the epididymis to the testis as occurring in cryptorchids, with 3 degrees of separation.

Hobday states that occasionally in the horse, the epididymis is found in the inguinal canal with the testicles oftentimes in the abdomen.

Badenoch (1946) reviewed the literature and reported 3 cases of complete failure of union occurring in a series of 42 adults operated upon for incomplete descent of the testis. He ventured the opinion that complete failure of union occurs only in association with undescended testis.

Blanke and Doerr (1942) reported an incidence of complete separation of testis and epididymis in a patient with undescended testicle and cited cases by Follin and Goddard in which there was a slight difference from the case they reported in that the testicles were undescended but the epididymis and vas deferns partially descended but retaining their connection by elongated and detinuated efferent ducts, or ductuli efferentis.

Lazarus and Marks (1947) described a complete separation of the partially descended epididymis and vas deferens with the testicle situated within the abdomen.

CONCLUSION

The embryological development of the urogenital system up to the point of separation into the urinary and reproductive systems has been briefly reviewed. The unusual operative findings in a patient with unilateral cryptorchidism, which revealed not only failure of union of the testis with the epididymis but also failure of union between the vas deferens and epididymis has been described. The ilterature has been reviewed without finding a similar instance of embryological maldevelopment.

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DISCUSSION

DR. GEORGE G. SMITH (Brookline, Mass.): I should like to say a few words about the surgery of megalo-ureter, or congenital dilatation—I don't know which this case should be called.

In 1945, I saw a girl of 7 who had been well up to 2 years before, when she began to have occasional attacks of fever; her general condition became less good, she lost weight, and she was unable to go to school. Pus was found in her urine. On examination, she proved to have 6 ounces of residual urine. Cystoscopy showed a thickened bladder wall, and the intramural portions of both ureters were not present. Whether they had been and had disappeared, I don't know, but both ureters appeared as round orifices, and there were no ureteral ridges.

I do not remember whether a cystogram was made. Both ureters were easily catheterized. Her NPN was 26, and catheterization showed a bilateral change in the ureters, which was much more marked on the left side than on the right.

I had not seen many of these cases, because we don't see many cases of urological diseases in children at the General. I looked through the literature casually to see what I could find about it. I came across an article by Hinman in 1925 or 1926, in which he described an operation for the treatment of megalo-ureter, consisting in first, nephrostomy until the kidney balance is re-established; at the time of the nephrostomy, the kinks in the upper ureter were straightened out. Then at a second operation, he straightened out the lower part of the ureter, excised the redundant portion, and reimplanted the ureter in the bladder.

I thought that in this case it would be unnecessary to do a preliminary nephrostomy, and events proved that that decision was all right. The lower end of the ureter was exposed by a suprapubic incision, and it was noted that the lower end of the ureter narrowed sharply and appeared to be twisted. The ureter was cut off at the narrow point and was stripped until it appeared to be about 4 cm. longer than it needed to be to reach the bladder wall without tension; consequently, about two inches of ureter were amputated. The ureter was implanted in the bladder wall in an oblique manner. The bladder was opened; the bladder outlet was examined, and it easily admitted the tip of the little finger. There was no evidence of sclerosis or obstruction. A 16 F. catheter was left up the left ureter; a 14 F. catheter was left up the right ureter. These were brought out through the bladder, which was drained suprapubically for something like a couple of weeks.

The child made a good recovery, and 15 months later she came to the hospital with an attack of pyelonephritis on the unoperated side. A cystoscopy was done; the left ureteral orifice appeared as a fairly round ureteral orifice in the lateral bladder wall. It was easily catheterized; the urine from that side was sterile. Retrograde pyelograms were done with these findings.

(Film) The left pelvis appears normal, the ureter narrow and without kinks. The lower part of the ureter still seems to have a bulge at the point just where it

empties into the bladder. The other ureter was not dilated any more than it had been in the first examination.

It seems to me that this condition should be discovered early and corrected, because the late results of this situation mean either vast dilatation of the pelvis and ureter, or total nephro-ureterectomy on the affected side.

Dr. John K. Ormond (Detroit, Mich.): I think the distinction Dr. Campbell made between true megalo-ureter and congenital hydro-ureter is a good one, and I want to show this cystogram of what I believe to be a true case of megalo-ureter. You see there is no evidence of any distension of the bladder. I could find no evidence in this child of any valves in the posterior urethra, and a cystogram gave this picture. He was 6 years old when he appeared. The only reason he consulted us was pyuria; he had no other symptoms.

I wanted to try Hinman's operation on this child. That was the only thing I could think of that might be of any avail. They consulted another man, and he advised against doing anything. He may have been perfectly correct.

We followed that child until he was 17 or 18, when he died. He lived a happy life, he went to school, he was an athlete, a leader in social affairs in his school. When he went to college, he continued to be athletic. One day he began to feel ill, and he died within 2 weeks. I don't know whether if we had started to tinker with him, he would have have been better off or worse off. I did have the opportunity of performing Hinman's operation on 1 child. It was a baby only a couple of months' old. I have forgotten what the symptoms were, but we found he had obstruction on both sides, and tortuous ureters like this. We removed part of the upper ureters and straightened them out and made a lateral anastomosis between the bladder and the ureter.

The patient has been under the observation of Dr. Mertz, and the last I heard he was still alive.

Dr. Higgins: I would like to ask Dr. Ormond if his patient gave any laboratory or clinical evidence of renal rickets.

Dr. Ormond: This patient? No.

Dr. Leon Herman (Philadelphia, Pa.): An observation we made recently might be worthy of record. Dr. Butterfield sent us a child of 8 years who had a congenital single kidney on the left side, with hydro-ureter. The patient, on careful inquiry, was found to have twitchings on the side of the body. On further questioning, I found the child at one time had fallen and became unconscious. It seemed evident that the child had Jacksonian seizures. They had been discounted prior to that time as possibly having something to do with the infection in the urinary tract. We sent the child to a neurologist who confirmed the diagnosis of Jacksonian epilepsy and did a pneumo-encephalogram and found the child had hemiatrophy of the brain in the pre-Rolandic area.

Whether central influences have any effect on these obviously neurogenic lesions is questionable. I thought this was worthy of record.

Another observation in a true case of megalo-ureter in a girl we followed since about the age of 10—she is now about 18—in which I did a meatotomy on one

ureter to see if back pressure transmitted through the bladder would cause more rapid destruction of the kidney than the obstruction incident to the neurogenic lesion. We have studied this child over and over and over again, and I can't see that either kidney is losing its function more rapidly than the other. I don't think there is any greater loss of function on the side that the meatotomy was not done on than on the side on which it was done. However, as usual in these cases, the patient has some pain in her back on voiding. So that I don't believe meatotomy in these cases serves to lengthen the life of the kidney tissue.

Dr. David M. Davis (Philadelphia, Pa.): There are two things I should like to remark on. First, in connection with Dr. Engel's case. I think the idea of a fistulous opening between the seminal vesicle and the urethra is a quite likely one. I have seen one such thing occurring in a colored gentleman from Haiti. This gentleman was, let us say, highly sexed. He had had more attacks of gonorrhea than he could enumerate, with many complications.

In the course of the examination I saw a hole in the floor of his prostatic urethra between the verumontanum and vesicle orifice. Moved by curiosity, as Dr. Engel was, I inserted a catheter and injected skiodan, and got a beautiful outline of the seminal vesicle and also a little indication of the ejaculatory duct running down to the verumontanum in the normal way. Evidently he had had an abscess in the vesicle which had ruptured into the prostatic urethra.

In regard to Dr. Campbell's paper, I was delighted with his fine objective presentation. There is so much about these cases that it is difficult to understand. I couldn't think of making any contribution except that sometimes I think obstruction is extremely difficult to demonstrate when present. However, the point that I thought might be interesting concerns experimental work done in connection with the operation of intubated ureterotomy, for which we are indebted to Dr. Keyes in his wonderful original case done over a quarter of a century ago. We have operated upon a number of dogs and sectioned the ureters at various stages after removal of two-thirds of the circumference of the ureter, followed by intubation. This permits us to study the growth of the ureter around the tube.

These sections show that while the epithelium reconstructs itself about the tube very nicely, making the ureter of normal size, the muscularis does not grow around the tube, so that we have a ureter equipped with muscle fibers over only a small arc of its circumference, let's say a quarter or a fifth. Nevertheless, such ureters perform their peristaltic functions perfectly well, as we have shown in many humans and in one dog where the peristaltic wave was actually seen to occur in the reconstructed ureter. Furthermore, the ureter does not undergo any dilatation in spite of the absence of musculature over a large part of the circumference.

Dr. Clark M. Johnson (San Francisco, Cal.): As this pyelogram shows, this child has a complete reduplication of ureters on the right side. The bladder was normal and there was no vesical neck obstruction. On the left there is one normal ureter and kidney. Cystoscopically, the lower ureteral orifice on the

right was normal, and leads, as you can see, to a single normal upper calyx. The upper ureteral orifice was wide open and the ureter dilated all the way to the lower and major portion of the kidney, which was hydronephrotic and was infected.

The presence of a normal and megalo-ureter on the same side without obstruction would seem against the theory of the neurogenic basis of megalo-ureter. At operation there was no obvious lack of musculature, either. The treatment instituted in this case was resection of the megalo-ureter and a portion of the hydronephrotic pelvis, with a side-to-side anastomosis with the normal ureter. This film taken 3 months later shows that there is now a near normal right kidney, with no hydronephrosis of the lower, major portion of the kidney.

This case will be reported in detail later, but I would like to make the suggestion that in most cases it is useless to attempt to ascribe a definite cause for megalo-ureters where obstruction is absent. After all, children are born with one large hand, ear or foot. The greatest importance in these cases is early and accurate diagnosis, and devising some surgical relief for a condition which, when bilateral, is at present fatal.

Dr. Vincent J. O'Oconor (Chicago, Ill.): In discussing Dr. Orr's paper, I should like to recite an experience which might be of interest along that line.

This is a patient about 30 years of age, a male, who was referred to me for an epididymovas anastomosis because he had been married for 6 years and numerous examinations of the semen had shown no sperm. He had a history of having had a so-called nonspecific epididymitis on the left side, and had never had gonorrhea. Palpation of the scrotum revealed two normally descended testes, one on each side, with a rather peculiar palpatory sensation of the right epididymis. This was the one which had not been inflamed. Whether the epididymis could be considered entirely normal, I don't know, although I could feel the body apparently in the usual position with the testes, with a globus major and globus minor distinctly outlined.

In opening up the scrotum, first on the right side, the one which had no history of having been infected, and dissecting out these tissues, I found a condition which I had never encountered before, and that was that the epididymis was distinct and apart from the body of an apparently normal testes, which was completely descended. Of course, there was no way in which I could perform the operation; apparently there was no way in which the sperm leaving the testes could get into the epididymis.

Then I was curious to see if the condition existed on the other side, the side that had the definite palpatory evidence of a previous inflammation and a history of epididymitis. The dissection on that side, of course, was considerably more difficult because of the scar tissue, and the epididymis was bound to the tunica vaginalis propria of the testes, but by carefully dissecting that away, we were quite definitely sure he had the same condition on the other side.

I have never gone into the literature of this thing, nor have I reported it, but I thought in view of the excellent presentation that Dr. Orr has made and the careful embryological review, the fact that he stated that some of the authors

have said this always occurred in undescended testes, this unusual experience is of interest.

Dr. Edward W. Campbell (Philadelphia, Pa.): I wish to thank Dr. Ormond for showing his picture of megalo-ureter of the type described by Saintu. Unfortunately, I have not had an opportunity to study the ureters of this type of anomaly. It was my hope in presenting this paper that some interest might be kindled to study ureteral sections, when available, for the lack of muscular development, for I feel it is not neurogenic in origin.

Dr. Johnson's case does not complicate this picture; instead, it helps to disprove the neurogenic theory. The presence of a normal and dilated ureter on the same side would not be the result of neurogenic dysfunction, but deficient muscular development could cause such a deformity.

The division of enormously dilated ureters into two etiologic groups lends itself to a more intelligent approach to the surgical management of these anomalies.

There is little to do for megalo-ureter, except a careful search of the posterior urethra for an obstructive factor. It may be possible, considering the work of Emmett, Thompson and Bumpus with neurogenic bladders, to resect the circumference of the vesical outlet to relieve some type of acalasia, as described by Perry, with symptomatic benefit.

The surgical approach to congenital hydroureter gives more promise because of an obstructive etiology, as suggested by Dr. Smith.

Dr. Ormond's suggestion of a lateral anastamosis to the bladder without disturbing the ureteral insertion into the bladder is something I have contemplated, but have been unable to try.

I have had no success with reimplantation of the large ureter into the bladder. The flabby wall permits the ureter to fold on its long axis, something like a folded umbrella, so that the lumen is constricted.

I have tried this in a 7½ year old boy who had a comparatively small renal pelvis. He rapidly developed an enormous hydronephrosis after transplantation. This fact was of interest for it helps to further substantiate the disassociation of anomalous pathology between the ureter and pelvis and may suggest something with regard to etiology.

Dr. George E. Hoch (New York, N. Y.): The thing that I am interested in mostly is, what can you do with them? I think there are a lot of them that are probably best left alone, but we have several cases. Quinby, you know, some years ago suggested massive pyelograms to determine whether or not these children had any deformities. The one child that I showed you 5 months old was cured by a vesical neck resection. The child was originally operated on abdominally, thinking it was a Hirschsprung's disease, because the ureter was so markedly dilated and could be so readily felt. One case that Dr. Bugbee had, a child who came with an acute infection after a dog bite, had a nephrostomy done in some other place and another nephrostomy done on the other side. The original side that was done a year before Dr. Bugbee saw this boy has now no function. The other side is perfectly all right. He also had a megalo-ureter.

He is living. He has an infection. I don't believe the infection that you get means too much if you have adequate drainage.

The point about most of these ureterovesical things is that they are infected and you do have to do something with them, because the infection per se doesn't mean too much. If you have adequate drainage the infection doesn't mean too much.

DR. LOUIS M. ORR (Orlando, Fla.): I would just like to thank Dr. O'Conor for his remarks. It is quite true in the literature there is mention that this particular failure of urogenital union has never been reported in other than cryptorchids.

HEMOLYSIS DURING TRANSURETHRAL PROSTATIC RESECTION

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Every urologist who resects the prostate gland down to the surgical capsule has doubtless encountered obscure reactions occurring shortly after operation. There may be some cyanosis at the onset, and the patient may or may not have chills and fever. He seems apathetic, and by the next morning has anorexia, sometimes with nausea and vomiting. The urea nitrogen of the blood rises rapidly; the characteristic oliguria is likely to be overlooked until bleeding subsides so that less irrigation is required. Anemia out of all proportion to the total loss of blood is typical, mild jaundice occurs early, and some hypertension may develop after a few days.

Slow recovery is usual, but most of my fatalities have followed such reactions. They seem to occur most often after prolonged operations with incision of the periprostatic venous plexus and considerable loss of blood, even though the blood is replaced during and immediately after operation.

Possible causes are numerous. The rapid loss of blood, even without hypotension, has been shown by Page and Corcoran to be capable of producing transitory azotemia in the dog, probably by inducing renal vasoconstriction. Similar changes may result from prolonged hypotension due to hemorrhage, shock or anesthesia. Renal damage may also follow the use of sulfonamides, transfusions of incompatible blood, and acute pyelonephritis. Although the reaction has unmistakably occurred in the demonstrable absence of all of these factors except the rapid loss of blood, the impossibility of preventing it by prompt and adequate transfusion even during operation; the disproportionate anemia, and the occurrence of jaundice when no transfusion has been given, all seem to rule out simple loss of blood as the causative factor.

Recently both Emmett and Foley independently have surmised that the cause of these reactions is to be found in the hemolysis of the patient's blood by the entrance into the venous system of the sterile water used as irrigating fluid during operation. Foley saw red jets coming from the ureteral orifices during a transurethral resection, and found a high level of free hemoglobin in the plasma immediately thereafter, thus proving his hypotheses that the urine was colored by free hemoglobin rather than by blood. Wardill reported the death of a patient with "transfusion kidneys" after transurethral resection without transfusion, but did not speculate on the cause of the renal lesion.

A more detailed discussion of the literature will be found in the author's papers on the subject in *Surgery* (January 1947) and the *Journal* of Urology (June 1947).

Severe intravascular hemolysis has long been known to affect the kidneys, and has been described repeatedly after reactions to the transfusion of incompatible blood, during blackwater fever, after severe burns, crush injuries, heat

stroke, sulfonamide and other poisonings, and as the result of infiltration of the uterine muscle by blood.

Hemolysis can be seen to occur within the bladder during transurethral prostatic resection as soon as the irrigating water comes in contact with the blood; if large veins are opened, it is evident that water may enter the venous system and cause much more extensive hemolysis. Stagnation in the pelvic veins may increase its severity. It seems logical that hemolysis will occur especially when brisk bleeding requires the use of fluid under higher than normal pressure to permit adequate vision, and when operation is prolonged. The usual hemoglobinuria is concealed by postoperative bleeding.

According to Flink, free hemoglobin is a threshold substance which appears in the urine when its concentration in the plasma exceeds 135 to 290 mg. per hundred cubic centimeters. It disappears from the circulating plasma in about 36 hours, approximately one-third being excreted by the kidneys while the remainder is taken up by the reticuloendothelial system which presumably converts it into the pigments that cause the characteristic jaundice.

When the free hemoglobin or one of its degradation products reaches the kidneys it produces a vasoconstriction which doubtless produces anoxia and prolongs the contact between the renal tubules and the hemoglobin, thus slowing its excretion and intensifying its toxic effects. If the kidneys have already been damaged by arteriosclerosis, hydronephrosis, or pyelonephritis, and if renal vasoconstriction is already present due to loss of blood or to a fall of blood pressure, the effect of free hemoglobin upon the kidneys may be increased during transurethral resection.

The changes in the kidney produced by hemoglobinemia include: vacuolation, necrosis, and desquamation of epithelium in Henle's loops and the distal convoluted tubules; pigmented casts in these and in the collecting tubules, and hemosiderin granules in the convoluted tubules ("transfusion kidney"). The nature of the pigmented casts is uncertain. They contain no iron, but give a positive benzidene reaction. It is not settled whether the resulting renal insufficiency is due to plugging of the nephron by these casts, or whether it results from a direct toxic effect of the free hemoglobin or its breakdown products upon the renal tubules, the casts being shed by the damaged tubular epithelium. Both are probably important. Anderson, Morrison and Williams have suggested that the tubular damage permits unselective reabsorption of the glomerular filtrate, thus explaining the oliguria and uremia. The changes are reversible unless too extensive, Flink having seen evidence of beginning repair about 5 days after the onset of severe experimental hemoglobinuria in the dog.

The level of free hemoglobin required to damage the kidneys seriously is quite high (3700 mg. per cent in Flink's dogs); as much as 50 gm. of hemoglobin have been injected into the human without producing evidence of renal damage despite a prolonged hemoglobinuria. However, these results were obtained in normal subjects, not in old men losing blood while under anesthesia.

The following abbreviated case report demonstrates that hemolysis occurring during transurethral prostatic resection can be a serious matter.

CASE REPORT

B. K., aged 68, was admitted to St. Barnabas Hospital on May 26, 1946, because of prostatism. His general state was good; the blood pressure was 160/90; there was a moderate sized benign hypertrophy of the prostate with 50 cc. of clear residual urine. Routine studies of the blood and urine yielded normal results; a urogram showed the upper urinary tract to be normal.

On May 28, 58 gm. of tissue were removed under spinal anesthesia supplemented with pentothal sodium. Because the blood loss totalled 600 cc., he was given 2 units of human plasma immediately after operation, and was placed in an oxygen tent owing to cyanosis erroneously thought to be due to a slight overdose of pentothal sodium.

That evening his blood plasma was examined because he had remained semistuporous despite a systolic blood pressure which did not fall below 120 millimeters of mercury at any time. His plasma was very dark red, although no quantitative estimate of free hemoglobin was made. Five per cent sodium bicarbonate was given intravenously and was repeated thereafter whenever the carbon dioxide combining power of the blood fell below normal.

By morning his blood urea nitrogen was 56. The hemoglobin, despite a blood loss which was about one-sixth of his blood volume, had fallen from 87 to 50 per cent, and he was nauseated and slightly jaundiced. Persistent oliguria followed, and by the sixth postoperative day the urea nitrogen was 109, there was peripheral edema, and the blood pressure had risen to 190/102.

Peritoneal lavage reduced the urea nitrogen to 69 in 3 days, but he died of cardiac failure and pulmonary edema. Pertinent findings at autopsy by Dr. A. J. Hertzog included: coronary sclerosis with cardiac hypertrophy and dilatation, basal atelectasis, and pulmonary edema. The kidneys weighed 215 and 235 gm. and were a uniform dark red on section. There was no hydronephrosis. The prostatic capsule had been perforated at one point, but there was no extravasation nor periprostatitis.

Microscopic examination of the kidneys (fig. 1) showed pigmented casts filling some of the collecting tubules. The convoluted tubules were dilated and their cells flattened, and the interstitial tissues contained collections of lymphocytes.

Comparison of these sections with two secured by renal biopsy on the third day after transfusion with incompatible blood in another patient, shows striking points of similarity (fig. 2).

Stimulated by this experience and by the statements of Foley and Emmett, we have been endeavoring to learn more about hemoglobinemia during transurethral prostatic resection.

Dr. E. T. Bell kindly restudied sections of the kidneys from 6 patients who died in uremia after transurethral resection at the University Hospital during the years 1941 through 1946, and found the characteristic pigmented casts and tubular lesions in two of them, although they had not been described in the original reports of the autopsies.

The effect upon the free hemoglobin of the plasma of intravenous fluids, surgical diathermy, and of open operations was next studied. The plasma hemoglobin was measured in 21 convalescent general surgical patients just before and immediately after the intravenous injection of 1000 to 1500 cc. of normal saline, of 5 per cent glucose in distilled water, of a combination of the two, and of

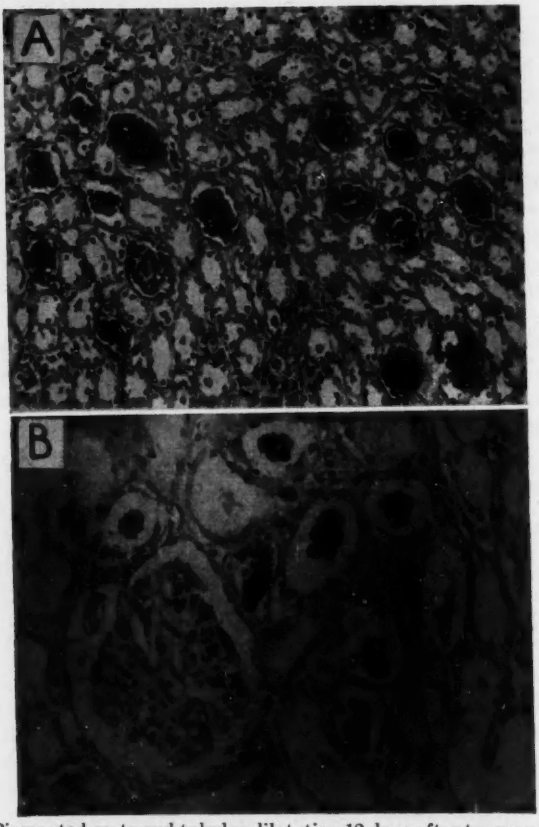

FIG. 1. *A*. Pigmented casts and tubular dilatation 12 days after transurethral resection. B. K., aged 68. Low power. Benzidene stain. *B*, Higher magnification of *A*.

10 per cent glucose in distilled water; in 8 neurosurgical patients in whom surgical diathermy was used; and in 13 patients subjected to general surgical operations (table 1). The free hemoglobin of the plasma in the 42 controls averaged 5.4 mg. per hundred cubic centimeters before, and 5.2 after the procedure in question. From this we may conclude that the injection of the ordinary fluids intravenously, the use of surgical diathermy, and ordinary open surgical operations do not produce a measurable amount of hemolysis. Free plasma hemoglobins up to 10 mg. per cent probably result from handling of the blood.

The plasma hemoglobin was also measured in 106 cases before and after transurethral resection with water as the irrigating agent (table 2). The preoperative level averaged 3 mg. per cent and the postoperative 45 mg. per cent, the latter being approximately 15 times the control value. While the highest

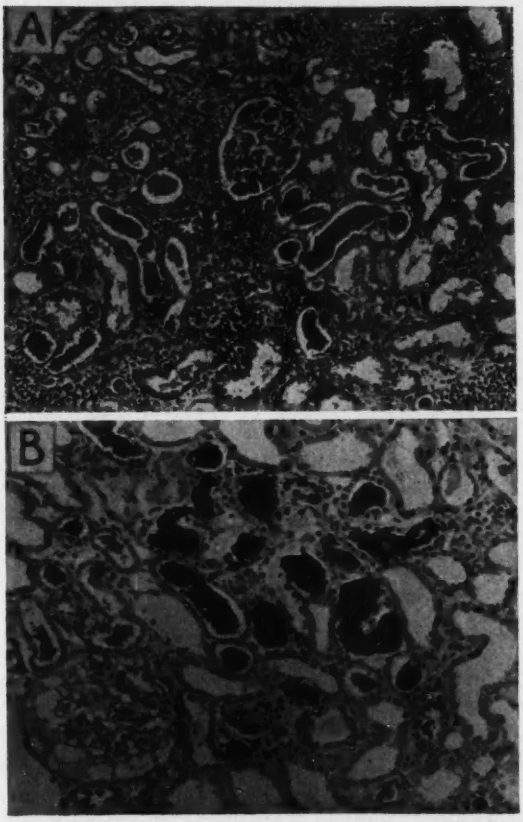

FIG. 2. *A*, Biopsy of kidney 3 days after transufsion with incompatible blood. Patient recovered. J. T., aged 21. Low power. Benzidene stain. *B*, Higher magnification of *A*.

level found (490) was insufficient to produce renal damage according to accepted standards, these findings appear significant.

Personal experience and a survey of the literature indicate that treatment of a severe hemolytic reaction is likely to be futile, there being no positive proof of the utility of such measures as alkalinization of the urine, transfusion with compatible blood, and so forth. The only procedure holding real promise seems to be peritoneal lavage, which may remove enough waste material from the body to permit the patient to survive until the kidneys recover; it is too dangerous to use unless the prognosis appears hopeless without it. Kolff's artificial kidney may come to have a place in such situations.

Preventive measures are therefore in order. The obvious solution is the use of a nontoxic irrigating agent which does not hemolyze blood. Normal saline

TABLE 1. *The effect of various non-urological procedures on the free hemoglobin of the plasma*

	BEFORE	AFTER
A. Intravenous Solutions, 21 cases		
Lowest	0	0
Highest	28	15
Average	5.5	5.2
B. Diathermy Without Irrigation (Neurosurgery), 8 cases		
Lowest	0	0
Highest	39	14
Average	5.5	3.4
C. General Surgery, 13 cases		
Lowest	0	16
Highest	23	16
Average	4	8

TABLE 2. *The effect of the composition of the irrigating fluid upon the free hemoglobin of the plasma*

A. Water		
Total Cases Studied		106
Preoperative Average		3.08 mg. %
Lowest	0	
Highest	28	
Postoperative Average		45.4 mg. %
Lowest	0	
Highest	490	
Average *Increase* during operation 42.3 mg. %		
B. Four Per cent Glucose		
Total Cases Studied:		
Preoperative		185
Postoperative		256
Preoperative Average		7.3 mg. %
Lowest	0	
Highest	74	
Postoperative Average		3.5 mg. %
Lowest	0	
Highest	194	
Average *Decrease* During Operation 3.8 mg. %		

cannot be used because being a good electrolyte, it diffuses and renders ineffective the diathermy current. Glucose, which has been widely used in the preservation of stored blood and, of course, for intravenous therapy, was suggested by Dr. Carl Ebert who had been using it for another purpose. We have used it, at

first in 5 and later in 4 per cent solution, in 256 transurethral resections in which special studies were made and tabulated (table 2).

The solution has been successful in preventing hemolysis, the postoperative plasma hemoglobin averaging below that in the controls, or 3.5 mg. per cent. Its use has given the most consistent tangible evidence that the irrigating fluid does indeed enter the circulation. The blood sugar has been measured in 78 nondiabetic patients just before and immediately after transurethral resection (table 3), with the interesting result that the postoperative averaged about 2½ times the preoperative value, having risen an average of 117 mg. per cent. The highest level found so far was 1079 mg. per cent. No glucose was given intravenously before or during these operations. Similar measurements in 104 cases with water as the irrigating agent showed practically no change in the blood

TABLE 3. *The effect of the composition of the irrigating fluid upon the blood sugar*

	PREOPERATIVE	POSTOPERATIVE
A. Four Per cent Glucose, 78 cases		
Lowest	69	76
Highest	143	1,079
Average	81	198
Average *Increase* During Operation 117		
B. Water, 104 cases		
Lowest	78	63
Highest	147	162
Average	87.1	86.9
Blood sugar not altered		

No frank diabetics included in computation.

sugar during operation. These figures prove that the rise in blood sugar cited above is due to absorption of glucose rather than to mobilization from stores in the body.

Increasing experience has convinced us of the great value of the use of 4 per cent glucose in the irrigating fluid. Untoward reactions have become the exception, and none of the type discussed earlier has occurred in over 300 cases. It seems likely that the cut surface of the prostate heals more kindly, and that the incidence of incontinence is lower, probably because the glucose solution does not irritate nor damage raw surfaces as plain water does. Mortality appears to have been reduced, but more experience must be acquired before figures can be quoted. There has been no instance of jaundice nor of disproportionate anemia; the need for postoperative transfusion has diminished strikingly.

To secure additional evidence certain comparisons were made between a series

of 109 consecutive cases in which water was the irrigating agent and a similar number in which glucose was used. The urea nitrogen rose in 12 per cent after operation with water as compared to 3.6 per cent with glucose. The average of those elevated in the first group was 67.5 mg. per cent and in the second group was 28.9. Three cases of jaundice occurred in the first group with an average blood urea nitrogen of 87 mg. per cent as compared to none in the second group. These figures are certainly suggestive.

Because of the possibility that virulent bacteria may be washed from the prostate into the circulation by the irrigating fluid, all of the patients in whom glucose was used were given penicillin and sulfadiazine for several days after operation, but the use of these drugs before glucose was employed did not reduce postoperative morbidity nor mortality. A series without chemotherapy is now being accumulated.

Since the continuous irrigation through the Foley-Alcock catheter used postoperatively might introduce fluid into the circulation if the outflow were blocked, normal saline is used.

There are certain disadvantages in the use of glucose. It increases cost slightly; it impairs vision because, since it does not hemolyze blood, the medium is a little hazy, but one soon becomes accustomed to this inconvenience, which will occur with any nonhemolytic agent. It makes gloves and instruments a little sticky, but is easily washed off. Instruments are not damaged. One must take care to measure the postoperative blood sugar in diabetics in order to gauge the dosage of insulin properly (one nondiabetic patient had a postoperative blood sugar of 1079 mg. per cent, and 8 had more than 400 mg. per cent!).

Because of these disadvantages Nesbit is now investigating the value of a solution of glycine, which is said to be cheaper and free from stickiness.

SUMMARY AND CONCLUSIONS

Evidence has been presented that water used as irrigating fluid may enter the circulation through open prostatic veins during transurethral resection, and hemolyze red blood cells.

This may lead to a severe anemia and to a hemoglobinemia which may cause toxic changes in the tubular epithelium and plugging of the collecting tubules, and so produce uremia. These effects are probably aggravated by renal vasoconstriction produced by rapid loss of blood, and by pre-existing lesions of the kidneys, such as arteriosclerosis, hydronephrosis, and pyelonephritis. The hemoglobinemia also causes jaundice. The reaction is similar to that seen after a transfusion with incompatible blood.

A fatal case is reported in which severe hemoglobinemia was followed by uremia and death. Pigmented casts were found in the collecting tubules, and were found on restudy in 2 of the 6 patients dying in uremia after transurethral resection.

Accepted therapy for severe hemolysis is probably futile, although peritoneal lavage may prolong survival enough to permit recovery of the kidneys to occur.

The hemolytic reaction can be prevented by the use of a sterile 4 per cent

solution of glucose as an irrigating fluid during operation. There is very often a striking rise in the blood sugar at the end of a transurethral resection when the irrigating solution contains glucose.

Transitory bacteremia resulting from the washing of bacteria from the prostate into the venous system may be treated prophylactically by administering penicillin and sulfadiazine before, during, and after operation.

The results thus far have been excellent in over 300 cases. No hemolytic reactions have occurred, and both morbidity and mortality seem to have been reduced.

The author wishes to acknowledge with gratitude the excellent assistance of his associates, Drs. B. A. Smith, Jr., E. A. Webb, G. B. Eaves, and David Anderson, in carrying out the studies briefly reported above, and of Dr. Gerald Evans and his laboratory staff in the University Hospital in making innumerable determinations of plasma hemoglobin and blood sugar.

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THE USE OF GLYCINE SOLUTION AS AN IRRIGATING MEDIUM DURING TRANSURETHRAL RESECTION

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Considerable interest has been aroused in the problem of the patient who, following a transurethral prostatectomy, manifests an anemia not commensurate with the operative blood loss, marked oliguria or anuria, loss of appetite, progressive nitrogen retention and jaundice.

Creevy believes this syndrome is due to intravascular hemolysis and has accredited McLaughlin with the suggestion that it is produced by water, used as an irrigating medium which has passed into the prostatic venous plexus during transurethral resection. Circumstantial evidence was provided by Foley (personal communication to Creevy) who observed spurts of red urine from the ureteral orifices during the course of a transurethral prostatic resection, and who subsequently found a high level of hemoglobin in the plasma of the patient.

In adhering to the principle of complete removal of the adenomatous gland by the transurethral route, the surgeon occasionally oversteps bounds and incises into the periprostatic venous plexus, with the result that brisk bleeding occurs. In such an instance the resectionist, in order to facilitate vision for the maintenance of hemostasis, may be forced to raise the level of the water reservoir inordinately high, thereby forcing the irrigating fluid into the venous system. Varying amounts of hemolysis might result from this course of events.

In proof of his thesis, Creevy found the average postoperative plasma hemoglobin level to be 59 mg. per cent in 9 patients upon whom he had performed transurethral prostatic resection using distilled water as an irrigating medium; whereas the control series exhibited no more than the average normal plasma hemoglobin level of 5+ mg. per cent.

Oliguria of this type has not been observed in any of the resected patients in the University of Michigan Hospital during the past 16 years. However, it is not at all unlikely that some of the postoperative morbidity which has occurred may have been due to unrecognized minor manifestations of the syndrome. Investigations have been made to determine if any subclinical hemolysis was taking place under conditions similar to those described by Creevy. Pre- and postoperative samples of plasma or serum were drawn through an 18 gauge needle, which along with its syringe had been previously cleansed with sterile isotonic saline. A pink to red discoloration of the plasma or serum in a sample of blood drawn 3–20 hours postoperatively was considered as indicative of intravascular hemolysis. In a group of 15 patients studied in this manner, there was no evidence of gross hemolysis in the preoperative samples, but in 3 patients there was gross hemolysis in the specimen examined postoperatively. None of the patients manifested any clinical signs of intravascular hemolysis. A serum bilirubin was determined in one of the patients exhibiting hemolysis and this was found to be

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 5, 1947.

0.1 mg. per cent. Elevation in serum bilirubin is not to be expected after minor intravascular hemolysis, for Ottenberg and Fox found no detectable rise in its level even after the intravenous injection of 5 gm. of free hemoglobin.

Granting the mechanism by which intravascular hemolysis is induced during the course of transurethral prostatic resection, interest is then attracted to the concomitant hemoglobinemia and to the hemoglobinuria with which it is so often associated.

In a review of the subject, Ross states that normally a level of 2–5 mg. per cent of "heme" containing pigment exists in plasma as a result of intravascular breakdown of erythrocytes. There appears to be a definite renal threshold for the excretion of hemoglobin, determined by the degree of saturation of the renal tubular cells. Yuile found hemoglobinuria where the plasma level exceeded 100 mg. percent; Gilligan et al. found it above 135 mg. per cent.

The mechanism by which renal damage results from severe intravascular hemolysis is poorly understood, but several factors bear mention. Although Gilligan et al. showed that intravenous administration of 16 gm. of pure hemoglobin to normal subjects produced no significant renal impairment, Mason and Mann demonstrated spasm of the renal blood vessels subsequent to intravenous injection of hemoglobin.

It was believed by many investigators that hemoglobinuria in the presence of an acid urine resulted in the formation of acid hematin which mechanically blocked the renal tubules. However, Bing working with dogs, showed no histologic renal lesions, and no significant variation in renal function after intravenous infusion of large amounts of hemoglobin and myoglobin, even with the blood at a pH of 6.9. Infusion of methemoglobin did produce demonstrable renal impairment. Pigmented tubular casts were found only in acidotic animals after renal failure had been initiated. He believes the acidosis accompanying the anuria may affect the respiratory enzymes of the tubular cells, accounting for impaired renal function. This factor would provide the indication for alkalinization when hemoglobinuria exists. He further believes that the renal vasoconstriction induced by hemoglobinemia may result in ischemia of the tubular cells accounting for their diminished function.

It is Ross' opinion that fatal renal damage is probably produced by shock-like levels of blood pressure, and by severe and prolonged reduction of blood flow through the kidney, the latter being accentuated by hemoglobinemia. Where an associated marked reduction of alkaline reserve exists, the formation of methemoglobin in acid glomerular filtrate may further add to already existing tubular damage.

In selecting an isotonic irrigating solution which will eliminate the risk of intravascular hemolysis, several properties must be considered:

1. It must be either non-electrolytic, or very weakly ionized, for a highly ionizable substance such as sodium chloride allows dispersion of the high frequency current, thereby inhibiting its cutting properties.

2. It must be non-toxic either by local tissue action or when administered intravenously.

3. It must be transparent so as not to interfere with visual acuity during the

performance of the operation. It must be understood that any isotonic solution used as an irrigating fluid will merely suspend the red blood corpuscles resulting in a slightly opaque medium, rather than the clear medium produced by the use of distilled water in which complete hemolysis occurs.

4. It must be relatively cheap to permit its use in large quantity.

Creevy has suggested the use of a 4 per cent glucose solution and previously has reported its use in 158 cases without any instance of hemolysis, but has pointed out that the solution makes the surgeon's gloves and instruments sticky, and if the operation is performed on a diabetic, careful observation of the patient's blood sugar level is required.

TABLE 1

CASE NO.	PREOP.	BLOOD UREA NITROGEN		
		30″ Postop.	60″ Postop.	120″ Postop.
		mg. per cent	*mg. per cent*	*mg. per cent*
1	21	19.1	18	18.1
2	10.8	12.7	12.1	15.7
3	17.4	17.4	14.7	15
4	14.1	17.6	14.9	17
5	21.8	20.6	18	20
6	11.9		10.9	12.7
7	17.4	16.1		15.6
8	13.1			13.7
9	9	8.9	8.3	9.4
10	17	15.3	13.1	12.1
11	20.2	15.3	17.9	19.7
12	17.2	13	13.4	13.7
13	14.1	14.1	12.2	14.2
14	22.8	20.6	21	18.5
15	13.2	12.1	13	11.1
16	10	10	10.8	11.3
17	10.4	9.4	10.1	11.2
18	8.6	9	9.7	8.2
19	16.1			12.2

We employed 4 per cent glucose solution in 9 instances without evidence of hemolysis, but because of the above noted objections, sought to find a more suitable agent. The amino acids should fulfill the criteria and because glycine is both abundant and cheap, it was chosen for trial. A 2.1 per cent solution of glycine is isotonic, so it was employed in 45 transurethral prostatic resections without demonstrable hemolysis.

Since glycine is believed to be metabolized in the liver with the production of urea, we sought to ascertain indirectly by the determination of blood urea nitrogen levels whether the use of glycine had any effect upon this product of metabolism. Blood urea nitrogen determinations were made immediately preoperatively, and at 30, 60 and 120 minute intervals following the initiation of the operation in 19 patients.

From the figures (table 1) it can be seen that no significant elevation in blood

urea nitrogen levels occurred following the use of glycine as the irrigating solution. However, from these findings it cannot be stated that no glycine gained entrance into the blood stream, for Landesman and Weinstein found no significant elevation in the blood urea nitrogen level even after injecting 50 gm. of amino acids (Amigen) directly intravenously.

The cost of using glycine in the irrigating solution is not great. The average volume of fluid used in our trial series was 12,000 cc per operation; entailing an average of 250 gm. of glycine. At the present price of $1.55 per pound, the glycine cost per operation was thus 75 cents. Recognizing the fact that red blood corpuscles will maintain their cell membranes intact even in the presence of solutions that deviate from isotonicity, determinations by means of the photoelectric colorimeter revealed that a 1 per cent solution of glycine does not produce hemolysis when in direct contact with red blood corpuscles. For this reason a 1.1 per cent solution has been employed in performing resections on 30 patients without demonstrable hemolysis. The 1.1 per cent solution costs only 38 cents per operation.

The preparation and sterilization of dilute glycine solution in large quantities comprise a formidable task in some hospitals that are not equipped with manufacturing pharmacies. In such institutions it may be found convenient to prepare a 20 per cent glycine solution which can be sterilized by autoclave in gallon bottles. This stock solution can be mixed with water as needed in the operating room.

The use of glycine solution does not interfere with determination of operative blood losses. Of course, the erythrocytes tend to settle at the bottom of the collecting receptacle necessitating a thorough mixing of the solution before taking up a sample for determination.

For the past 2 years we have discontinued routine bladder irrigations following transurethral resection, believing this procedure to induce persistence of bleeding. Following this principle we have encountered less postoperative blood loss and have found evacuation of blood clots from the bladder only rarely necessary. The indwelling urethral catheter used postoperatively is attached to an intermittent irrigating system filled with sterile distilled water, which is available for irrigation should there be any question as to the patency of the catheter. Since irrigations are not carried out during the period when the prostatic veins may still be patent, it has not been considered to be necessary to use glycine in the postoperative care of the patient. However, it probably would be more safe to maintain a reservoir of physiological saline, glycine, or glucose in the irrigating system for the above purpose, rather than distilled water or boric acid solution when irrigations are carried out.

CONCLUSION

It has been demonstrated that the irrigating solution employed in the operation of transurethral resection of the prostate may pass directly into the prostatic veins and result in hemolysis of varying degrees.

Excessive hemolysis, from such a cause, in conjunction with operative shock

or marked blood loss acting upon kidneys damaged by chronic pyelonephritis and/or arteriosclerosis, may result in a clinical syndrome which is manifested clinically by anemia, oliguria or anuria, and uremia. This syndrome may end fatally.

The phenomenon due to this cause can be prevented by the use of any isotonic non-electrolytic irrigating solution.

A 2.1 per cent solution of glycine, an amino acid, is isotonic and has been found to satisfy the proposed criteria; it has been employed successfully in 45 transurethral prostatic resections without demonstrable gross evidence of intravascular hemolysis.

A 1.1 per cent solution of glycine, while not isotonic, has been found nonhemolytic in vitro, and has been used in 30 resections without producing hemolysis. The use of the lower concentration is economical as well as safe so its employment as an irrigating solution during transurethral prostatic resection is advised.

Note: Since this paper was read, the 1.1 per cent solution of glycine has been used in over 200 additional patients undergoing transurethral prostatic resection with no ill effects and without demonstrable hemolysis.

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PERSISTENT ARTERIAL HYPERTENSION[1]

C. RUTHERFORD O'CROWLEY AND (by invitation) H. S. MARTLAND

Of the many perplexing pathologic problems is the entity of so-called generalized constriction of the arteriolar vascular system having an unknown cause, signified by elevation of blood pressure with its paucity of symptoms that progresses like cancer until it produces its fatal complications in the form of congestive heart failure, coronary occlusion, cerebral hemorrhage, renal insufficiency or general visceral failure.

This condition has always been placed in the category of diseases of the blood vessels. This form of high blood pressure of unknown etiology which is termed essential, primary or idiopathic hypertension, has become more specific in recent years since there has been clearly delineated those forms of high blood pressure of known etiology termed secondary or symptomatic hypertension which clinicians have observed in glomerulonephritis, acute, subacute and chronic, in congenital polycystic kidneys, atrophic pyelonephritis, coarctation of the aorta, arteriovenous fistula, aortic regurgitation, complete heart block, denervation of the carotid sinus, increased intracranial pressure, toxemias of pregnancy and the various endocrine gland disorders as hyperthyroidism, pituitary basophilism and adrenal paraganglioma. And added to this the urologist has established the so-called "surgical kidney" of unilateral renal disease (tumor, calculous, infection, anomaly and obstruction) as a cause of secondary hypertension. With recognition beyond doubt of the various forms of secondary hypertension the treatment where possible is logically that of the underlying cause with resultant alleviation of the hypertension; the basic pathogenesis, however, in the production of the hypertension from these known causes is not always known.

The perplexity of the nature of essential hypertension is even more intriguing since in this condition there is wanting not only knowledge of the fundamental pathogenesis in the production of hypertension, the pathology of which is assumed to be a generalized constriction of the arteriolar vascular bed, but also a *cause* that may account for the mechanism of the process of hypertension. The importance of essential hypertension as compared to secondary hypertension is realized not only in the fact that it is the leading cause of death but also that 95 per cent of all hypertension is essential hypertension, the seat of which investigators have sought to discover is some organ or system, assuming, at least, a single cause for idiopathic hypertension. Investigators in various medical and surgical specialties have endeavored to specify the cause with logical conclusions of conjecture and theory. The incrimination of the kidney as the focus in the production of essential hypertension has been a popular subject in recent years. The investigation of the kidney has at least brought forth the unquestionable fact that unilateral renal disease may cause secondary hypertension which may be alleviated by surgical treatment. That the kidney is the cause of the all impor-

[1] Read at the annual meeting of American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

tant, common, essential hypertension is not at all conclusive. Of importance, nevertheless, is the fact that since many urologic lesions of obstructive or infectious nature are associated with hypertension, it is justifiable to consider before classifying a patient as hypertension of unknown origin to prove normal the entire urinary tract from a urologic standpoint. The urologic surgeon, therefore, takes on the responsibility to determine those selected cases of hypertension that can be cured by surgery since these cases fall in the category of symptomatic or secondary hypertension in which the high blood pressure is only a symptom whose prolonged presence may result in grave complications. It is also to be realized that before consideration of the radical surgical procedures now in vogue for hypertension such as various types of sympathectomy and excision of adrenal tissue, the urinary tract should be ruled out as a possible cause of hypertension. Though abundant evidence exists that hypertension in patients with pyelonephritis and other unilateral renal diseases is not uncommon, and that nephrectomy in advanced unilateral disease has reduced blood pressure permanently it remains that the factor in this disease that produces hypertension is not known and nephrectomy is not justifiable in early cases.

Thus, by means of clinical studies of the kidney in hypertension the urologist has revealed added renal lesions in the production of hypertension and has confirmed other renal pathologic entities as a cause in the mechanism of hypertension. But the problem is hardly solved, for the renal lesions in hypertension as is seen clinically make up an almost insignificant etiology, and, although the kidney has been successfully and justifiably incriminated in secondary hypertension, the kidney as a participant in the pathology of essential hypertension has also been rightly included, and the internist and surgeon are directing their activities in the channel of renal origin.

Conceding the accepted factors which maintain normal arterial blood pressure, investigators single out the factor of peripheral resistance that is a product of the viscosity and velocity of the blood and caliber of the lumen of the peripheral vessels. That the other factor, cardiac output, which is a product of the heart rate and stroke volume which is dependent on the force of myocardial contraction and venous return, can raise blood pressure is nevertheless ruled out of the pathogenesis of essential hypertension. It is assumed that in essential hypertension that the increase in the peripheral resistance exists in the form of generalized constriction of the arteriolar vascular system. That the kidney is responsible for this generalized pathological state has been the aim of many investigators to prove. Through the remarkable studies of such workers as Goldblatt, Page, and others the renal origin of essential hypertension has become an attractive subject. Goldblatt's demonstration that lasting hypertension occurs after partial compression of one or both main renal arteries of animals by a metal clamp has renewed interest in the relationship of kidneys to increased arterial pressure, and that renal ischemia is in some way responsible for experimental hypertension.

In 1939 Page demonstrated that constricting cellophane perinephritis produced chronic renal hypertension. He hypothecated that renal ischemia is due to

peripheral vasoconstriction due to the presence in the blood of a pressor substance (*angiotonin*) derived from interaction of renin (an enzyme-like substance) from the kidney with an activator in the blood plasma.

In the past decade much energy has been stressed to unfold the mystery of this deep-seated pathological condition. It can hardly be said that the unsuccessful discovery of the cause is due to meager exploration in this field. Many advances have been made and several outstanding experimental conclusions have been deduced. That the kidney maintains a most popular position in the role of hypertension pathogenesis is evident. There are many questions unanswered so that the treatment, whether medical or surgical, still remains for the most part empirical.

31 Lincoln Park, Newark, N. J.

DISCUSSION

DR. HERMAN L. KRETSCHMER (Chicago, Ill.): For the information of our friend Martland, may I say that my diagnosis of the case would be that his friend who wants everybody x-rayed has a lot of stock in some film company.

I am delighted to hear Dr. Martland's paper. He has been here before, and I think, like old whiskey, he gets better every time he comes. This presentation today tops his previous presentations, his paper on "Aneurysms in the Brain," and his paper on "Polycystic Kidney." I think it is delightful to hear him inject into this discussion a large measure of common horse sense. I think the people on this hypertension business are running wild, and I think that papers of this type should tend to keep people on an even keel.

The urologist sees many patients, at least we do in Chicago; we have patients referred to us for the cure of hypertension because they have some renal lesion.

I think the work of Goldblatt, while highly commendable, has been very unfortunate in its by-products. A great many people are being operated upon for so-called Goldblatt kidney, and the desired result, namely, a drop in the blood pressure, is not obtained.

Interesting in this connection are the figures published by Dr. Bright, of the Mayo Clinic, some years ago in which he showed that in the ordinary patients with ordinary renal disease there is no drop worth mentioning in unilateral nephrectomy.

I was very much intrigued by the papers of Dr. Creevy and Dr. Nesbit, and I should like to ask them, in closing the discussion, to tell us the height of their irrigating stands. Do they use very much pressure when they irrigate? It seems to me, aside from the fact of using water, which hemolyzes the blood, that another factor is important, in my opinion, and that is whether you have your irrigator high or low. It seems to me high pressure has something to do with this problem. For us, we always have stressed the fact that the irrigators must be low.

I think they are to be complimented on two splendid presentations in calling attention to a condition that in all probability can be prevented, and, as Dr. Martland said, prevention in hypertension and prevention in hemolyzing the blood.

DR. BENJAMIN S. BARRINGER (New York, N. Y.): This is the second time that Dr. O'Crowley and Dr. Martland have presented papers before this Association, and this is the second time that Dr. Martland has journeyed down to us, the first time at Stockbridge, and the second time here, to give us the results of his work. This Association is greatly honored to have Dr. Martland come here and do this for us.

Anyone who has visited Dr. Martland's amazing museum in Newark realizes the enormous amount of material which he has collected and part of which he has used to give us presentations such as this one this morning. I do not wish to discuss it further, but I simply wish to say that I will use it as my bible in the future when I think of hypertension personally and in patients.

Dr. George R. Livermore (Memphis, Tenn.): If we had heard nothing but these three papers, we would be repaid for coming to this meeting.

The fact that the use of distilled water causes reactions of chill, fever, anorexia, nausea and vomiting—most of us have believed that they were the symptoms caused by urinary fever; that they were due to absorption from the denuded area in the bladder neck and prostatic urethra rather than hemolysis, as has been so ably demonstrated to us.

I shall use the glucose solution first and later the amino acid as the former will be obtainable in any hospital.

I believe the reason I have had no higher mortality than other resectionists is due to the fact that like Herman Kretschmer, I do not elevate the irrigator more than 2½ feet above the patient. Also, when the hemorrhage is so profuse following each cut, you waste more time in fulguration than in resection; we have discontinued the resection, put in a Foley bag, pulled it down for a few minutes to control the hemorrhage and repeated the resection at a later date.

Dr. J. Dellinger Barney (Boston, Mass.): I agree with Dr. Livermore, that the trip down here would have been well worth while just to have heard these three papers.

I would like to augment what Dr. Kretschmer says about the height of the irrigator apparatus by asking the speakers to tell us how much fluid they think it is safe to put into the bladder at one time. Bladders will vary, of course, but to what extent is it safe to distend the bladder with the fluid, regardless of the height of the irrigating tube?

Dr. Leon Herman (Philadelphia, Pa.): May I ask Dr. Martland what evidence there is pathologically to support the theory of essential hypertension in children? We recently had a 4 year old boy with Bell's palsy and a running ear in the hospital. Routine studies showed he had a blood pressure of 220/150 over 140. The neurologist said there was nothing intracranially. The pediatrician finally induced me to explore the adrenals, which were normal. One kidney was slightly larger than the other. I decapsulated the kidneys and the blood pressure dropped to 140, and now is back to 200. The diagnosis remains unknown. We have given him antagonistic drugs to adrenalin. It doesn't affect his blood pressure. I was convinced before and remain convinced that there is nothing the matter with his adrenals.

Does Dr. Martland have any evidence to prove that true essential hypertension of the malignant type occurs in children?

Dr. David M. Davis (Philadelphia, Pa.): Having now become a fellow of the society, I hope that I may be pardoned for becoming a purveyor of old fashioned and antiquated ideas, but I cannot help reminding the society that there is another way of preventing hemolysis after prostatic operation. That is, with enlarged glands where the resection is likely to be prolonged, a well-conducted prostatectomy is much better.

Dr. Louis Orr, Jr. (Orlando, Fla.): I have enjoyed Dr. Creevy's and Dr. Nesbit's papers immensely. In view of the fact that Dr. Creevy mentioned Dr. John Emmett in some of the correspondence, and Dr. Emmett and Dr.

Thompson have had relatively the same incidence with the cold punch that they have in the production of hemolysis, I wonder if we could hear from Dr. Thompson.

DR. GERSHOM J. THOMPSON (Rochester, Minn.): We have been carrying on some experiments similar to Dr. Creevy's. We find that hemolysis does occur in a fair proportion of cases. We study the plasma pre- and postoperatively, and can see considerable hemolysis in some cases. It does not seem to make much difference whether the prostate is large or small, as much hemolysis might occur in resections involving only a few grams of tissue as in resections of large amounts of tissue. In some of the largest resections there has been no hemolysis whatever.

DR. H. S. MARTLAND (Newark, N. J.): I do not believe I can answer that question or make a possible guess as to the cause of the hypertension in this young child.

Dock and others have recently called attention to a number of stillbirths, newborns and infants who have been autopsied and show marked narrowing of the coronary arteries and occlusive lesions typical of early arteriosclerosis.

Therefore, we may expect to find in persons over 45 years of age, a considerable number who have probably had arteriosclerosis in some form throughout their lives and who eventually develop hypertension. Osler stated years ago that some people are born with bad tubing.

Likewise, in civil life we medical examiners have for years noted sudden deaths from coronary arteriosclerosis in men as young as 20 to 25 years of age. Army experience in World War II has verified this well-known fact.

In the case in question, the possibility of whether the child had a previous acute nephritis or pyelonephritis which is the basis of the hypertension, although careful studies seem to have ruled this out, or whether congenital heart disease, especially coarctation of the aorta is a possible explanation.

DR. C. D. CREEVY (Minneapolis, Minn.): There wasn't time to explain the origin of the idea of hemolysis during resection. I learned of it at a meeting in St. Paul both from Dr. Emmett and from Dr. Foley. Foley had seen red jets issuing from the ureteral orifices during transurethral resection in a patient whose urogram the day before had been normal. He had the hemoglobin of the plasma measured and found it very high; he had the idea, but did nothing about it.

Emmett told me that he got the notion from W. McLaughlin, a former Fellow in Urology at the Mayo Clinic. In any event, it was a very good idea, and I I am ashamed that I didn't think of it myself.

For convenience, we have kept the glucose on hand as a sterile 100 per cent solution, which is diluted just before use. Nesbit's glycine is probably better, because it gets away from the stickiness of glucose, but glucose was superior for our purpose because its entrance into the circulation can be determined readily by measuring the blood sugar before and after operation.

Someone mentioned measurement of the blood loss. This is simplified by adding an equal quantity of tap water to the irrigating fluid and stirring it to produce hemolysis before the acid is added.

In so far as not irrigating the postoperative patients is concerned, Dr. Nesbit doesn't work in private hospitals in Minneapolis.

Concerning Dr. Kretschmer's inquiry, I use varying pressures. Our irrigators can be raised and lowered, and I use the lowest pressure which will permit clear vision, and that is never very high. Since hemolysis is as likely to occur during resection of a small gland as a large one, I do not believe that one can prevent it either by using a low irrigating pressure, or, in reply to Dr. Davis' suggestion, by replacing transurethral resection with prostatectomy. You can be sure that it can be done in that fashion, but I question the desirability of that approach.

In reply to Dr. Barney's inquiry about how much fluid can be put into the bladder, I work with a finger in the rectum much of the time, and when the bladder feels full, I let the water out.

Dr. Orr mentioned the matter of other causes of hemolysis during resection. In our control series, a small number of patients was subjected to neurological operations with surgical diathermy; none of these patients exhibited any evidence of hemolysis.

Dr. Reed M. Nesbit (Ann Arbor, Mich.): A year ago at the Stockbridge meeting of this society, Creevy discussed informally with me this problem and asked me how many patients we had seen at Ann Arbor who had died with anuria following transurethral resection, and I told him that I had never seen a patient die in that fashion. However, when I went home, we started making determinations of evidences of hemoglobinemia on our patients. I had thought perhaps that the level of the irrigator used during operation might make the difference in his observations in his clinic with those in our clinic.

Of the series of cases which we investigated, in which the irrigator is always at the lowest possible level, 20 per cent of our patients did show evidence of intravascular hemolysis. Since using these various prophylactic measures, we have observed no evidence in any case of intravascular hemolysis.

STUDIES IN THE DISSOLUTION OF URINARY CALCULI: EXPERIMENTAL AND CLINICAL ASPECTS[1]

LINWOOD D. KEYSER, PHILIP C. SCHERER (by invitation) AND LAWRENCE W. CLAFFEY (by invitation)

Probably the first to dissolve a urinary calculus on a scientific basis was Crowell who demonstrated the dissolution of certain cystin stones by alkalinizing the urine and irrigating the stone-containing kidney with alkalies and mercurochrome.

Randall achieved a modicum of success by using 1 per cent phosphoric acid to clean up alkaline encrusted cystitis and small bladder stones. In 1932 one of the authors accomplished probably the first almost complete disintegration of calcium phosphate stone in the kidney by catheter irrigation with dilute aqua regia and by acidifying the patient's urine with an acid diet and dilute aqua regia by mouth.

Higgins then developed the use of acid ash diet and acidifying drugs together with massive doses of vitamins A and D (chiefly in the form of cod liver oil). He achieved numerable successful dissolutions of alkaline earth stones by this method. Also some acid stones were dissolved by an alkaline ash diet and alkalinizing drugs. Urinary acidification and alkalinization do at times dissolve certain soft concrements, but it was soon found that while occasionally good results were obtained, more frequently these regimens failed.

Albright, Suby, Sulkowitch and others at the Massachusetts General Hospital, after extensive studies of calcium-phosphate-carbonate calculi and of the calcium-phosphorus metabolism, found that citric acid mixtures disintegrated calcium stones not only by their acid reaction but by the formation of a complex calcium-citrate ion. The citrate anion has a specific chemical avidity for the calcium cation. From Albright's original "buffered" citrate solution Suby developed solution G[2] and solution M.[3]

These solutions G and M have been used by catheter irrigation and not a few examples of successful calculus dissolution have been reported. These dissolutions involve for the most part soft pultaceous calculi of calcium carbonate and phosphate. Uratic and oxalate stones have been particularly resistant.

THE SIGNIFICANCE OF THE ORGANIC FRAMEWORK OF CALCULI

It is a somewhat strange but noteworthy fact that up to the present practically all efforts at calculus dissolution have been based on some form of chemical

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 6, 1947.

[2] Solution G—Citric acid monohydrate ..... 32.5 gm.
Magnesium oxide anhydrous ..... 3.84 gm.
Sodium carbonate anhydrous ..... 4.37 gm.
Distilled water ..... 1000 cc.
The reaction of this solution is adjusted to pH 4.

[3] Solution M—Citric acid monohydrate ..... 32.5 gm.
Magnesium oxide anhydrous ..... 3.84 gm.
Sodium carbonate anhydrous ..... 8.84 gm.
It is somewhat less acid and not quite so irritating as Solution G.

attack on the crystalline matter composing the stone. Investigators have uniformly failed to appreciate or to take any consideration of the organic framework in which crystals are intimately deposited, and by which they are, may we say, cemented together. It would seem that any rational attempt at calculus dissolution should include a primary or at least a concomitant attack on this cementing organic framework. With its partial or complete disintegration, crystalline dissolution should proceed more rapidly with solvents capable of dissolving the crystalline matter.

The senior author had for years attempted to dissolve stones removed at operation or autopsy by irrigating them in vitro with various mineral and organic acids and other reagents such as G solution and sodium hexametaphosphate. Each of these reagents brought about prompt surface dissolution of most alkaline stones, but after this the calculus was found to be covered by a mucinous organic substance, which apparently interfered with further action of the solvent. This gelatinous envelope we assumed to come from the above mentioned organic framework in which the stone forming crystals are deposited. The importance of this component was emphasized by Ebstein, Lichtwitz, Schade and others but as noted has been forgotten by workers in this field. Its chemical structure is not readily ascertained by present methods. Therefore to dissolve or destroy this organic envelope became our immediate problem.

In 1941 the senior author sought the aid of Dr. P. C. Scherer, professor of physical chemistry at Virginia Polytechnic Institute, Blacksburg, Virginia. L. W. Claffey, a graduate student in Dr. Scherer's laboratory, became interested, and the three of us outlined a program of attack on the problem. We decided to test the efficacy of various solvents and reagents on both the organic and crystalline matter of urinary calculi in vitro.

From our own service and from urologic colleagues we secured something over one hundred fifty stones. First an accurate qualitative analysis of the calculus was made by sawing it in two parts, using the sawdust for analysis. The freshly cut surface of each part was coated with a thin layer of DeKhotinsky cement so that the reagents used could not penetrate the stone by means of the exposed layers. It was necessary to do this so as to duplicate the conditions prevailing in the uncut stone. Each half of the stone dried at 105° C., was weighed in a weighing bottle before the cement was applied, again after. The prepared stones were then subjected to treatment with solvents.

APPARATUS USED FOR IRRIGATION OF THE CALCULI

See figure 1. The washed stone was placed in a Gooch crucible (11) which was provided with a closely woven linen filter cloth (10) and the crucible, after weighing was suspended in a 50 cc beaker (9) by means of glass hooks (8). The beaker was supported in a glass funnel (12) which was connected to a large glass reservoir bottle (13). In a glass battery jar (1) of about three liter capacity was placed the "G" solution to be used. On the surface of this was placed a wooden float (2) which had been waterproofed by Bakelite varnish.

To one side was placed a small bore (5 mm.) siphon tube (4) the hydrostatic

head of which could be regulated by moving it up and down in the float. The weight of the siphon tube was counterbalanced by weight (3). This type of constant flow apparatus was devised by Sullivan and proved to be capable of accurate adjustment. The siphon flow was started and the delivery adjusted to a rate of 10 cc per minute, which was carried through the guide tube (5) into the Gooch crucible, over the stones (7) and into the beaker. The beaker on filling

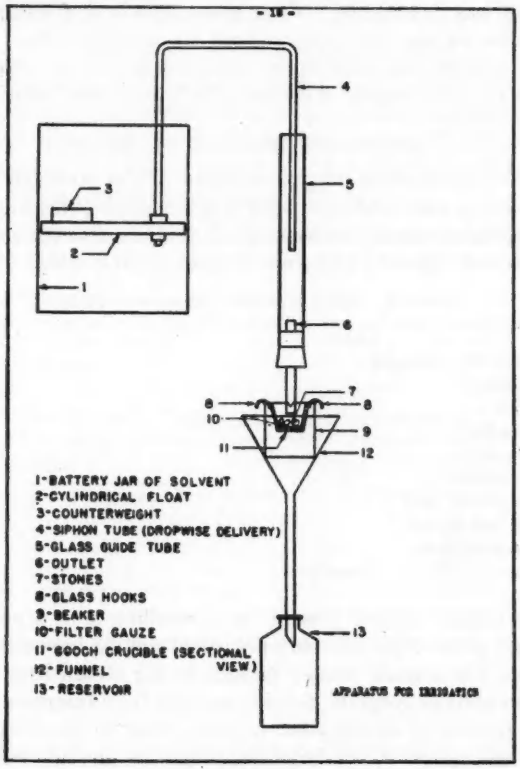

FIG. 1

kept the level of the liquid in the crucible well above the stones and the overflow from the beaker passed into the reservoir by way of the funnel.

After the desired irrigation period the stones were washed with distilled water until free from salts, the crucible and contents were dried to constant weight at 105° C. and the loss in weight was recorded as per cent dissolution.

The filter cloth was provided to prevent the loss of any finely divided material resulting from disintegration of the stone. In many cases the stones were completely disintegrated into a fine white powder of the consistency of precipitated chalk and such cases were recorded as completely disintegrated.

PRELIMINARY STUDY OF SOLVENTS

As a preliminary study urinary calculi taken at random were irrigated in the apparatus with 10 of the recommended solvents found in the literature. In no case was more than the outer surface of the stone dissolved and no disintegration of the calculus ensued. The results of the experiment are shown in table 1. Each stone was treated for 6 hours with the solvent and the weight before and after treatment was determined. From these data it was assumed that either the citrate buffer, or the G solution showed the most promise. In the subsequent work G solution was used as the standard solvent for crystalline matter, although we realized its limited effect on oxalate and urate calculi.

ENZYME TREATMENT OF CALCULUS

As a result of the preliminary experiments it was concluded that aqueous solutions of the type used could not penetrate the layers of organic matter and so could not alone bring about complete dissolution, or disintegration, of the calculi. A search was begun to find some reagent capable either of attacking and

TABLE 1. *Effect of solvents on urinary calculi*

Solvent	*Per cent Dissolution*
Citrate buffer (1) (Albright)	12.50
G solution (Suby)	12.60
1% citric acid	0.54
Phosphate buffer	1.00
1% tartaric acid	3.15
5% sodium chloride	1.12
1% metaphosphoric acid	0.09
Benzoic acid (saturated)	8.50
1% disodium phosphate	6.60
1% dihydrogen potassium phosphate	1.40

destroying the organic matter present, or of swelling it to a point where subsequent passage of the aqueous solutions would not be impeded. Making the assumption that the organic matter present in the stones had originally been dispersed in the urine as lyophilic colloids and had been desposited in the calculi through some process of dehydration (a point open to much question) it was thought that restoration of the lyophilic properties should result in swelling, possibly followed by dispersion.

In seeking an agent capable of bringing about this reversal, attention was drawn to the enormous activity, chemical and physical, of the enzymes. In the hope that such substances might be helpful, 0.5 per cent solutions of such enzymes as were on hand were prepared at the proper pH for maximum activity by using buffer solutions. The prepared stones were placed in weighed Gooch crucibles, provided with the filter disk of closely woven linen, and were then immersed in the enzyme solutions contained in beakers for 2 hours. The temperature was maintained at 38° C. for this period. At the end of the treatment, the stones were washed with distilled water and subjected to irrigation with

G solution for 6 hours in the apparatus described. The results of the preliminary experiments are given in table 2.

As a result of these experiments it appeared that urease definitely increased the solubility of calculi above that of G solution alone. Trypsin also appeared to act in a similar manner but not to the same extent. Following this observation a systematic investigation of the effect of urease as an aid to dissolution was made and is described below.

TREATMENT WITH G SOLUTION ONLY

In order to determine the effect of irrigation with G solution without pretreatment with enzymes, a number of calculi from each anion group was subjected to irrigation in the apparatus described for 6 hours, using G solution alone. After washing and drying, the loss in weight was recorded along with any observed disintegration and the results are given in table 3.

TABLE 2. *Effect of enzymes on solubility of calculi (preliminary)*

Enzyme	*Per cent Dissolved*
Urease	100.0
Pepsin	5.8
Diastase	8.1
Trypsin	43.8
Papaya	19.1

TABLE 3. *Dissolution with G solution alone*

GROUP	NO. OF STONES	AVG. PER CENT DISSOLUTION	DISINTEGRATION
Phosphate	12	25.5	None
Carbonate	11	23.6	None
Urate	4	23.5	None
Oxalate	7	13.4	None

None of the stones disintegrated and the dissolution took place only on the surface or outer layer.

OPTIMUM TIME OF ENZYME TREATMENT

In table 2 it was shown that pretreatment of calculi by urease solution for 2 hours brought about a marked increase in dissolution and disintegration. In the present experiments the samples were treated with 0.5 per cent urease solution at 38° C. for times ranging from a few minutes up to about 25 hours. Each stone was then subjected to irrigation with "G" solution as described above. The average results are given in table 4.

The results were very irregular but appeared to indicate that a 15 minute treatment gave as good, or better, results as a prolonged period. In all subsequent experiments a 15 minute pretreatment formed the basis for the experiments.

UREASE TREATMENT AND G IRRIGATION

One hundred calculi prepared as already described were subjected to a 15 minute treatment with 0.5 per cent urease solution at 38° C. were washed with

distilled water, and were then irrigated for 6 hours with G solution. The decrease in weight was reported as *per cent dissolution* and the *degree of disintegration* into an impalpable powder was noted. If the material broke down completely to a powder, the degree of disintegration was recorded as "complete". If a still solid portion of the stone remained, or if relatively large fragments were still present, it was recorded as "partial disintegration". If the stone retained its form and resisted crushing with the fingers, the degree of disintegration was noted as "none". The results of all experiments with urease are recorded in table 5.

Of the 100 stones treated, it was found that 9 resisted disintegration. However, 4 of the resistant stones were composed wholly of oxalates and the characteristics of G solution make it a relatively poor solvent for oxalates. Two of the remaining stones contained oxalates, and phosphates, or urates; and the last

TABLE 4. *Effect of time of enzyme treatment on dissolution*

Time of Treatment	*Average Per cent Dissolved*
15 minutes	93.2
30 minutes	56.5
1 hour	68.0
2 hours	67.2
4 hours	31.3
8 hours	35.5
21 hours	28.2
25 hours	52.0

TABLE 5. *Urease treatment and irrigation with G solution*

GROUP	NO. OF STONES	AVG. PER CENT DISSOLUTION	DISINTEGRATION		
			Complete	Partial	None
A—Ca, NH_4, Mg, $-PO_4$	30	55.6	29	0	1
B—Ca, NH_4, Mg, $-CO_3$, PO_4	21	68.4	21	0	0
C—Ca, $-CO_2$	3	36.0	3	0	0
D—Ca, Mg, NH_4, PO_4, Urate, Xanthine	4	42.0	1	1	2
E—Ca, NH_4, —Urate	2	37.8	2	0	0
F—Ca, —Oxalate, CO_2	1	63.4	1	0	0
G—Mg, Ca, NH_4, PO_4 Urate, Oxalate	4	75.9	4	0	0
H—NH_4, Mg, Ca, PO_4, CO_2, Oxalate	16	59.2	14	1	1
I—Mg, Ca, NH_4-PO_4, Urate, CO_2	5	58.3	4	1	0
J—Ca, —Oxalate	5	7.6	1	0	4
K—Mg, NH_4, PO_4, Oxalate	7	40.3	6	0	1
L—Mg, Ca, NH_4 —Urate, Oxalate	2	11.7	2	0	0

two showed a dissolution of nearly 92 per cent but did not disintegrate into a powder during treatment. All of the resistant stones were characterized by extreme hardness and high density.

PAPAYA TREATMENT AND G IRRIGATION

A solution containing 0.5 per cent of papaya at a pH of 7.0 was used in place of urease. In other respects the treatment of the calculi was the same as described for urease. The results are given in table 6.

TRYPSIN TREATMENT AND G IRRIGATION

The same procedure was employed as for urease but using a 0.5 per cent solution of trypsin at pH of 3.8 for the pretreatment. The results are given in table 7.

ANALYSIS OF RESIDUES

All the residues of the calculi contained organic matter and in nearly all cases all of the phosphates were removed but some of the carbonates remained. In a few instances, urates and oxalates were removed and in other cases, they remained in the residue.

The presence of organic matter in the residues may be taken to indicate that the disintegration of the stone did not depend on the conversion of the organic matter by the specific action of the enzyme, to a soluble product. Simple swelling so as to permit the entrance of the solvent G solution would result in removal

TABLE 6. *Papaya treatment and irrigation with G solution*

GROUP	NO. OF STONES	AVG. PER CENT DISSOLUTION	DISINTEGRATION		
			Complete	Partial	None
Phosphates	4	19.3	0	3	1
Carbonates	4	18.8	0	3	1
Urates	1	20.8	0	0	1
Oxalates	4	8.6	0	4	0

TABLE 7. *Trypsin treatment and irrigation with G solution*

GROUP	NO. OF STONES	AVG. PER CENT DISSOLUTION	DISINTEGRATION		
			Complete	Partial	None
Phosphate	4	27.0	1	3	0
Carbonate	5	43.8	1	4	0
Urate	1	48.8	1	0	0
Oxalate	3	26.2	1	2	0

of most of the inorganic constituents and resulting disintegration, without the necessity of complete removal of the organic matter.

ACTION OF UREASE ON THE ORGANIC MATTER FROM STONE

In order to attempt to determine the action of urease on the urinary colloids forming the matrix of the calculi, such organic matter was separated according to the following procedure.

Stone No. 167, a large bladder stone, which showed from chemical analysis the following components: NH_4, Ca, Mg, carbonates, oxalates, phosphates, and unknown organic material, was ground to a fine powder and placed in G solution for 24 hours. At the end of this time the bottle was shaken vigorously and the contents allowed to settle for 10 minutes. The cloudy solution above the sediment was transferred into a cellulose membrane sac and dialysed first against distilled water and then against N/10 HCL. The colloids remaining in suspension were

separated from the liquid by centifuging the contents of the membrane. The extracted material was entirely organic in nature, and contained nitrogen, carbon and oxygen. It failed to give the usual reaction for protein. The material was of a dark brown color, completely insoluble in water and ether, and contained no sulfur. The material changed from a dark brown to a brilliant yellow when treated with concentrated nitric acid. Dilute ammonium hydroxide changed the color from a brilliant yellow to a deep red-brown. This colloidal material was placed in a 0.5 per cent solution of urease at a pH of 7.0. The mixture was placed in a fermentation tube and maintained at a temperature of 38° C. After 6 hours, the colloids had swollen to *about five hundred times their original volume.* The color changed from a dark brown to a flocculent, translucent material.

Apparently the action of urease on the colloids is hydrotrophic in nature and results in the swelling and at least partial solution to a point where some of the organic material can pass the filter medium. That partial solution took place was indicated by the appearance of an organic colloidal precipitate on saturating used G solution with ammonium sulfate.

DISCUSSION

Investigations by Snapper have shown that urine is a supersaturated solution of many substances which are practically insoluble in water. He states that these water insoluble substances are made soluble in urine by the presence of hydrotrophic compounds. Among such compounds are hippuric acid, salicylic and mandelic acids, and urea. Snapper holds that certain colloids are hydrotrophic and believes that chondroitin sulfuric acid and nucleic acid are among the more important hydrotrophic substances. Our investigation indicates that urease is a hydrotrophic substance that activates the urinary colloids, changing them back to their former state of dispersion. Urease is known to be a very active enzyme and will decompose its own weight of urea in 1.4 seconds. It will liberate 129,000 mg. of nitrogen from urea-phosphate solution in about 5 minutes at room temperature. It is also known that enzymes owe much, if not all, of their catalytic properties to their relatively enormous surface area, a property due to their high state of colloidal dispersion. This investigation indicates that the hydrotrophic properties of urease swell or disperse the colloids in the calculi and thus aid in the disintegration of calculi by permitting dissolution of the inorganic constituents along with destruction of the organic matrix.

The optimum time of enzyme treatment seemed to be about fifteen minutes. However the results in table 2 are so inaccurate as to permit only a rough guess as to this. Perhaps a series of controlled experiments on carefully chosen stones of the same composition might permit a more accurate determination of this point.

Papaya and trypsin were apparently not as effective as urease in this series of experiments, although the action appeared to be of the same nature as that of urease. It is possible that the particular preparations of these enzymes may not have been as active as desirable and further experiments should be carried out with these, and other enzymes.

At the present time further studies are being carried out to determine the

chemical nature of the organic matrix of the stone. Numerous other enzymes are being tried as we obtain them from commercial and biochemical sources. Two of these enzymes in preliminary study seem to be effective, viz, orthozyme 10 (Rohm and Haas) and ficin proteinase (Merck). In vitro their activity does not seem so marked as that of urease. However they may supplement the activity of urease and the senior author has used these two enzymes in clinical trial.

CURRENT CLINICAL EFFORTS AT STONE DISSOLUTION

Before considering possible clinical application of the preceding laboratory investigation, we should review briefly certain present day attempts at dissolving stone in situ. We have mentioned the use of acidifying and alkalinizing diets and drugs, of phosphoric acid, aqua regia and G solution.

Now Snapper, Benedein and Pollak on the basis of their experimental work with hydrotrophic substances, advocated oral administration of sodium benzoate and glycocol to form hydrotrophic hippuric acid in the urine. They reported some clinical success in diminishing phosphaturia and in diminishing renal colic. We personally have tried the benzoate-glycocol therapy in several instances and while it has seemed to diminish crystallinuria, no dissolution of calculus has followed, nor have we been impressed with any marked salutary effects on rapidly stone forming kidneys.

Schorr of Cornell University in 1945 showed that aluminum hydroxide gels (amphogel) would prevent about 90 per cent of the absorption of phosphate from the alimentary tract and that it would, in addition to this, decrease the excretion of calcium. By the administration of amphojel (120 to 160 cc) daily thus calcium phosphate excretion in the urine could be definitely decreased.

Scott, Huggins and Selman found that patients with urinary stone secrete less citric acid in the urine than normal individuals. Now Schorr found that estrogens such as estradiol benzoate in doses of 2000 R.U. daily would diminish the excretion of urinary calcium and would increase the urinary excretion of the citrate ion. This citrate ion excretion would carry the calcium through in solution especially in alkaline mediums and prevent deposition of calcium phosphate. In clinical treatment a low calcium phosphate dietary, together with estrogens and amphojel was outlined. This procedure is now under extensive clinical trial but no detailed report of success or failure has yet been made.

Greta Hammarsten in 1937 produced primary calcium oxalate calculi in rats by diets deficient in vitamins and in magnesium and calcium with maintenance of acid urine. Only a few points of her extensive studies can be mentioned. Vitamin deficiency produces excessive urinary calcium excretion. Calcium deficiency in the diet produces increased urinary calcium excretion, from mobilization of the calcium of the skeleton. Magnesium deficiency increases calcium absorption and increases urinary calcium excretion. The excretion of calcium in the urine is least when fat soluble vitamins and a rich calcium magnesium dietary are given and where the urine is maintained at pH 6.2. If higher acidity is maintained the calcium excretion is increased, as has been noted by Albright

and his coworkers. It should be noted that Hammarsten's findings in rats are not consistent with the fact that biochemists teach us that magnesium administration in the human being actually increases urinary calcium excretion. Thus from Hammarsten's work one might try a hypothetical dietary high in vitamins, high in magnesium and calcium, low in phosphorus with maintenance of the urinary pH at 6.2. If we could then add Schorr's estrogen and amphojel administration, the answer to our problem might appear at hand. Unfortunately this is not the case. These basic experiments in the animal and physiologic laboratories while interesting and worthy of clinical trial have many controversial features. Furthermore they have not yet been used singly or in combination in human beings with reported success.

We do recognise however that the ideal stone solvent will probably be some diet, drug or hormone to be given by mouth or parenterally so as to secrete a stone solvent urine from the kidney. These experiments point out the possibility.

RETROGRADE DISSOLUTION OF CALCULI WITH FERMENTS AND G CITRATE SOLUTION

As a result of the above physio-chemical studies we began to apply the principle of using ferments to attack the organic matter and G solution to dissolve the crystalline material in 1942. Irrigation is provided through ureteral catheters or if present through nephrostomy tubes. Many arrangements of such apparatus have been devised, each investigator as a rule using his own improvisation. The set-up which the senior author believes most closely approaches the conditions used in the chemical laboratory has been in use for several years. We call it the "three catheter irrigation" system. The illustrations demonstrate the simplicity of its component features (fig. 2). A large 2 gallon tank is suspended alongside a 300 cc salvarsan flask, the large tank containing Suby's G solution and the smaller flask the ferment solution. The two containers each with a glass drip interposed are attached to a Y tube which is in turn connected by a rubber tube to one of three ureteral catheters which have been passed to the pelvis of the stone containing kidney. The two catheters not attached to the inflow tube serve as a double drain to carry the urine from the kidney. A Foley retention catheter is placed in the bladder to take care of bladder drainage.

If one of the outflow catheters becomes clogged by urinary salts it is irrigated with G solution to dissolve encrustations and attached to the irrigating tube. Thus it becomes the inflow catheter, while the catheter which has recently been feeding fluid into the kidney now becomes an outflow tube.

At first while getting the apparatus in working order we allow 2 per cent boric acid-saline solution to flow into the kidney pelvis. Then this is replaced by the G solution which is allowed to run at a drip rate of 30 to 40 drops per minute for several hours. This inflow is then interrupted by clamping the tube between the G solution flask and the Y tube. The ferment solution is allowed to flow at the same rate for 30 minutes. The ferment solution is then stopped and G solution started again. At night while the patient is sleeping a 6 hour rest period is given by clamping off both G and ferment solutions.

CLINICAL MANAGEMENT

The ferments used have been 0.5 per cent urease (Arlington), 0.5 per cent orthozyme 10 (Rohm and Haas) and 0.25 per cent to 0.5 per cent ficin proteinase

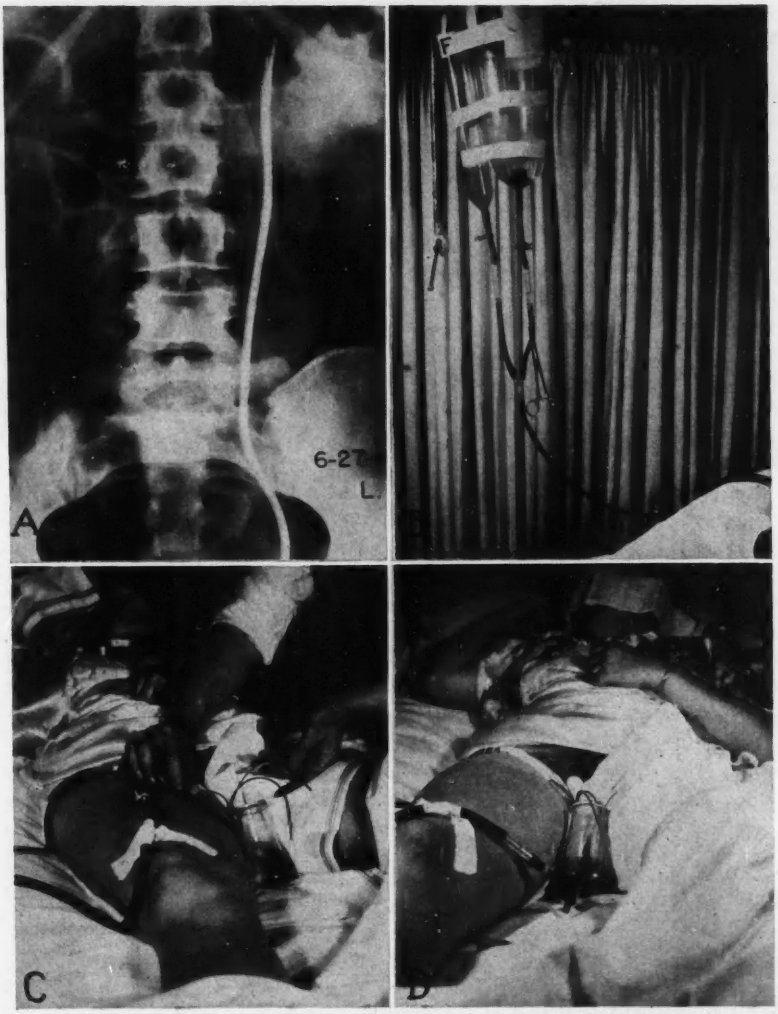

FIG. 2. *A*, Three No. 5 or 6 catheters passed to renal pelvis. *B*, Irrigation tanks, smaller F for ferment solution; larger G for solvent solution. *C*, Detail of attachment of irrigator to inflow catheter. *D*, One inflow and two outflow catheters. Foley catheter conducts drainage from bladder.

(Merck). No effort is made to sterilize the ferments. They are weighed from the container and suspended in sterile normal saline, with sterile apparatus. Cultures are made and if pathogens are found a new batch is made. The fer-

ment is kept in the refrigerator until ready for use, when it is allowed to warm to room temperature.

The selection of the case for stone dissolution is important. The chemical nature of the calculus may be surmised if a stone previously passed or removed has been analyzed. Otherwise we must rely on the contour and density of the calculus by x-ray and the urinary and blood findings, e.g. the reaction and calcium and uric acid content, to give us a lead as to whether alkaline or acid irrigant should be used. Oxalic and uratic calculi will almost always resist dissolution. The method is not yet ready for application to stones which had otherwise better be removed surgically nor should it be used in cases with a single kidney or with a poorly functioning diseased kidney on the opposite side. It may be well applied for dissolution of fragments left at operation or of calcareous material showing up early recurrence after operation.

The patient must be intelligent, able to understand the working of the apparatus, and psychologically able to endure the ennui and boredom of lying in bed, working with the set-up for at least 7 to 10 days at a time. The nature of the procedure and the risks involved should be explained to the patient and his family.

At cystoscopy under pentothal or spinal anesthesia a No. 10 F. or 11 F. bougie is used to dilate the ureter. After this 3 No. 5 F. catheters are passed usually with ease. Occasionally the ureter will require several dilatations before multiple catheters can be used. The patient must tolerate indwelling catheters without any reaction. The 3 catheters must all be draining freely, and the urine must be clear. The irrigator is then attached and tested with 2 per cent boric acid solution, after which the ferment and G solution are started.

Pain, irritability, poor drainage of the outflow catheters, gross hematuria and especially fever are danger signals for immediately stopping irrigation with any solution. In patients intolerant to indwelling catheters the procedure must be stopped.

The use of sulfonamides or antibiotics, especially penicillin, while the irrigation is in progress has been our practice since the advent of these drugs.

If after 10 to 14 days x-ray shows no definite evidence of a smaller stone shadow, we stop this therapy and advise the patient that the effort has failed.

CASE REPORTS

We have now used the ferment-G solution irrigation in 18 cases of urinary calculi and alkaline encrusted cystitis. It is excellent in cleaning up encrustations about surapubic and nephrostomy tubes. Several failures have been noted with renal calculi. One was a stag-horn calculus in an infected kidney. Nephrostomy above and ureteral catheter drainage below were instituted. The stone diminished in size remarkably but staphylococcal infection so increased that nephrectomy became necessary. Two cases of Proteus infection failed to respond.

The use of this technique in dissolving recurrences after operation is shown in the following 2 cases.

Mrs. F. W. G., 1942, R.H. No. 59237, aged 48 years. Left pelviolithotomy

with nephrotomy tube. Recurrence of calcium deposition after 1 month. Urea splitting Proteus. Irrigation through nephrostomy tube above and ureteral catheter from below for 8 days with urease 0.5 per cent and solution G. Disappearance of calcareous mass after 8 days. No recurrence after 1 year. Interval dilatation of ureter and irrigation with G solution. Death from cerebral hemorrhage. Autopsy showed chronic pyelonephritis. No calcium deposits. Urine cultures remained positive for several months. Sparse growth of E. coli after 9 months and E. coli obtained from autopsy culture.

Mrs. O. P. W., R.H. No. 63777, 1943, aged 63. Bilateral renal calculosis; left pelviolithotomy, July 1943. Calculus, Ca phosphate-oxalate. Urine pH 6, pyocyaneous infection. Recurrent shadows left pelvis, September 1943. Multiple catheters with irrigation 0.5 per cent urease and G solution 8 days.

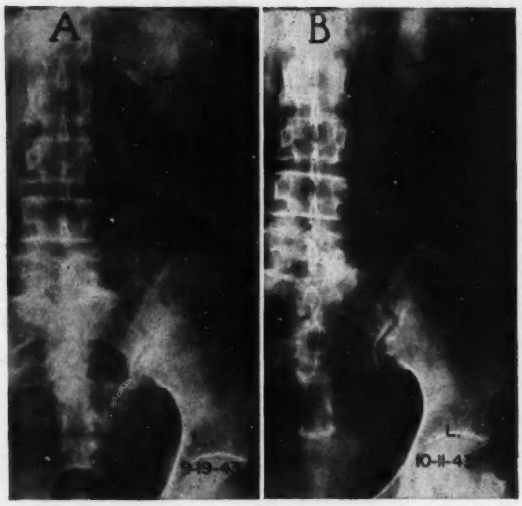

FIG. 3. Recurrent calcareous mass in left kidney 2 months after left pelviolithotomy. Dissolution 3 weeks after irrigation.

Shadows disappeared. Rt. pelviolithotomy and pelvioplasty November 1943. No recurrence and urine pus free and culture free after 3 years. Periodic renal lavage with G solution for 24 hours by syringe method every 3 months for 1 year after operation. See figure 3.

Its use in the dissolution of a large soft stone in the left kidney is illustrated by this case.

Mrs. J. P., R.H. No. 70372, 1946, aged 27 years. Stone left kidney. Staphylococcus (slight urea-splitting). Urine pH 7. Stone appears to arise from renal parenchyma. Dilatation of ureter with bougies. Three No. 6 F. catheters passed to left pelvis and irrigator attached. Irrigation for two 10 day periods 0.5 per cent urease, 0.5 per cent orthozyme 10 (Rohm and Haas) and 0.5 per cent ficin proteinase (Merck) used on separate days for ½ hour and irrigation with G

solution continued for 12–18 hour periods. Stone shadow definitely diminished in size after 2 weeks and almost disappeared after 4 weeks. After 6 weeks rest period patient returned to hospital for a third 8 day period of irrigation. Mild exacerbation of pyelonephritis after discontinuing irrigation. Stone shadow had entirely disappeared and has remained absent for 9 months. Periodic renal lavage at 3–4 month intervals. Urine now free of pus and cultures are sterile. See figure 4.

The efficacy in dissolving multiple small calculi in the right kidney is illustrated by the history of this patient.

Mrs. R. M., R.H. No. 73166, 1947, aged 46 years. Multiple small stones, right lower calyx; dilatation of ureter. Three No. 5 F. catheters passed. Irrigator attached. 0.5 per cent urease, orthozyme and ficin proteinase on separate

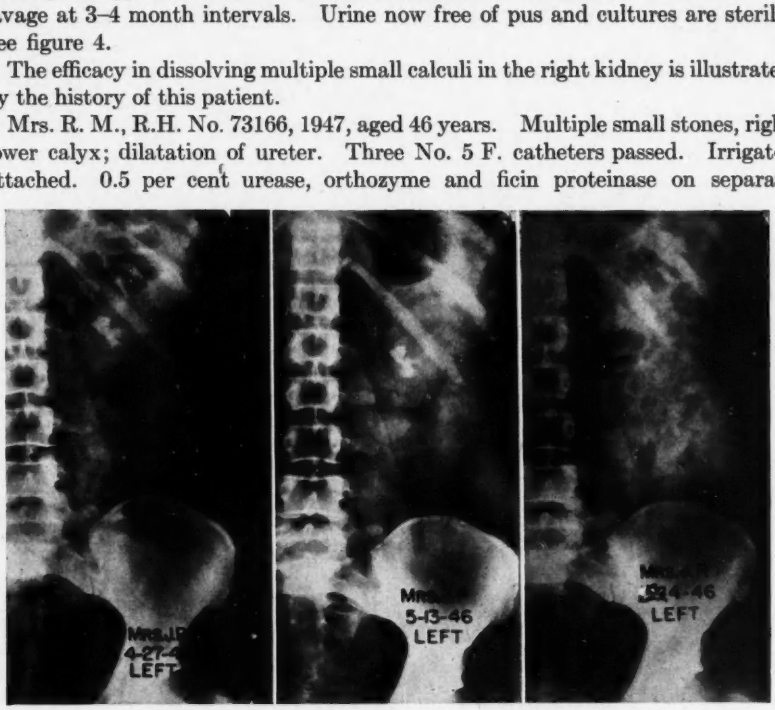

FIG. 4. Dissolution of large soft stone in left kidney over several weeks with ferments and G solution.

days followed by 16 hour daily irrigation with G solution. Continued 9 days. Urine pH 6.5; calcium studies normal. Urine shows non urea-splitting gram negative bacillus. Questionable diminution of size of stones after 2 weeks. Patient placed on high vitamin regimen, with Schorr low phosphate diet, premarin, magnesium oxide and amphojel. Stones have disappeared after 2 months. Urine is pus free. Still scant growth bacilli. Stones may have passed but no history of colic and no calculi recovered.

Other cases are under study at the present time.

SUMMARY

We have attempted to attack the organic matrix of urinary calculi by treating them in vitro with ferments preliminary to irrigation with solvent solutions such as solution G.

Of the enzymes studied to date 0.5 per cent urease is the most effective, with orthozyme, ficin proteinase and trypsin showing a comparable but lesser degree of activity.

These enzymes act by a digestant action on the organic matrix (colloids) of the stone. This is partly dissolved and partly swollen so that the cementing substance which binds the crystalline matter together is loosened and renders the latter more susceptible to dissolution by crystalline solvents.

We present positive evidence that such enzyme treatment in vitro accelerates and intensifies the action of G solution especially on alkaline calculi.

In a small series of clinical cases there is presumptive evidence that this enzyme effect may likewise accelerate and intensify the effect of G solution and similar solvents in the dissolution of stones and calcareous material in the human being.

Full evaluation of this regimen must await further clinical experience.

Finally we point out the long overlooked fact, that the organic framework of stone is an object of attack equally important to the crystalline matter, in the problem of calculus dissolution.

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RENAL TUBERCULOSIS: DOES IT HEAL CLINICALLY?[1]

JAMES C. McCLELLAND, KENNETH H. DAVIS AND ERIC MASSIG

Each surgeon who is called upon to treat renal tuberculosis will be faced with a problem similar to the following. A young girl aged 17 years presented herself with the history that 1½ years before she had had a diagnosis of left renal tuberculosis made by a competent urologist. In the investigation there were a few pus cells and tubercle bacilli coming from the affected side. The retrograde pyelogram showed no change and there was no frequency. The urologist had advised her to return for observation at a later date as the lesion in the kidney was very early and it might heal of its own accord. The following questions come to mind. Was this the correct advice to give? Would the open lesion discharging pus and tubercle bacilli heal? Having once diagnosed renal tuberculosis, can one forecast healing of this area? If pus cells and tubercle bacilli are coming from a kidney and no change in the pyelogram can be detected, should one feel hopeful of a clinical cure?

At the Toronto Hospital for the Treatment of Tuberculosis at Weston, Ontario during the past 16½ years we have had an opportunity to study 400 cases of genito-urinary tuberculosis. We would like to state, briefly, the clinical and pathological findings of the kidneys removed at operation together with those from autopsies. Our examination has been that used in every day practice in the pathological laboratory, special care being taken to note small lesions. It has not been possible to make the large number of microscopic serial sections, as done by Medlar in his monumental work, but our investigation has been confined to a careful practical study of the specimens presented. A thorough search of each kidney was carried out and we believe that very few if any lesions have been missed. Microscopic study of special areas was done where necessary.

Nephrectomy was carried out in 57 of these patients. Their symptoms varied and pyelographic changes varied from no change to marked cavitation of the parenchyma. It has been interesting to compare the clinical and x-ray findings with the pathological findings.

Autopsies were done on 40 of these patients. The local tuberculous process was confined to the genital tract in 7 and to the kidneys in 33. The lesions varied from tiny ulcero-cavernous lesions to complete autonephrectomy. Grouped together the surgical and autopsy specimens have provided an opportunity to make gross and microscopic studies of 105 tuberculous kidneys.

PATHOLOGICAL FINDINGS (TABLE 1)

In reviewing the pathology of renal tuberculosis in this series of 40 autopsies and 57 surgical specimens, the outstanding lesions seen were those of progressive tuberculous involvement and destruction of one or both kidneys. These may be grouped into 3 main categories; viz., the early solitary or multiple caseous

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 6, 1947.

lesions; the intermediate ulcero-caseous lesions with single or multiple cavitation, and the late tuberculous pyonephroses.

Of the autopsies, 2 cases had gone on to autonephrectomy, and 13 presented late bilateral or unilateral tuberculous pyonephrosis, and more recent solitary caseous or ulcero-caseous lesions with cavitation of the other kidney. In 15 other cases, ulcero-caseous lesions with cavitation in various stages of formation were seen, and in the remaining 7, only genital lesions with no evidence of renal tuberculosis were present.

The surgical specimens as a group presented lesions which were obviously of a less advanced stage and probably of much shorter duration than in those found at autopsy. More recently specimens have been obtained in which very early single caseous lesions giving rise to bacilluria were found. This series presented two autonephrectomies and only 12 pyonephroses as compared to 28 specimens with ulcero-caseous lesions and cavitation, 7 solitary or multiple caseous nodular

TABLE 1. *Pathological findings*

	AUTOPSY	SURGICAL
1. *Early*—Caseous lesion—solitary or multiple	—	7
very early ulcero-caseous	—	6
very early single focus	—	2
2. *Intermediate*—Ulcero-caseous lesions—single or multiple cavitation	15	28
3. *Late*—Pyonephrosis	13	12
4. *Autonephrectomy*	2	2
5. *Genital lesions only*	7	—
6. *Autopsies*—One kidney removed—remaining kidney non-tuberculous	3	—
	40	57

lesions, 6 of the very early ulcero-caseous type without cavitation, and 2 cases of very early single caseous foci involving the tip of a single papilla.

This study reveals a composite picture of the course of renal tuberculosis from the early tiny caseous lesion through succeeding stages of progressive involvement and destruction of kidney with cavitation going on to tuberculous pyonephrosis and ultimately in some instances terminating in autonephrectomy.

We believe that the initial lesions were of hematogenous origin and consisted of microscopic foci of typical tuberculous granulomatous cellular reaction. At that stage they probably presented no clinical or laboratory manifestations sufficient to attract the attention of the urologist. They progressed to a later stage with caseation and destruction of kidney parenchyma and the presence in the urine of pus cells and bacilli without attending clinical symptoms. It is conceivable that such early cellular lesions might have healed by scar formation, but the fate of the lesions in the cases of this series appears to have been one of progressive evolution to stages in which the possibility of healing did not exist. No healed tuberculous foci were demonstrated in the material examined, and in the final analysis, one must conclude that if healing does not take place during

the initial cellular phase of the tuberculous process, the subsequent course will be that of progressive involvement of one or both kidneys to the stage in which renal function has become grossly impaired, resulting in a state of uremia and death.

CORRELATION OF PATHOLOGICAL FINDINGS WITH CLINICAL INFORMATION

From the foregoing paragraphs it is apparent that clinical healing could not be expected in the vast majority of the kidneys examined. There was, however, the small group of 8 cases of very early caseous or ulcero-caseous lesions which were found in the surgical specimens. Special attention was paid to these 8 cases for two reasons: firstly, they were early lesions which would be more likely to heal than any of the others; and secondly, they were single foci which would lead to extensive involvement if healing did not take place.

An analysis of these 8 very early cases showed that all were clinically unilateral at the time of operation. Four presented no bladder symptoms while 3 had mild frequency, and one suffered from cystitis of moderate severity. Pus and tubercle bacilli were found on microscopic examination and culture of bladder urine, but gross pyuria was reported in only 1 patient. Ureteral specimens were positive in each case. Retrograde pyelograms were normal in 4, dilatation of the kidney pelvis and ureter was present in 2 while the remaining 2 showed slight irregularity of one calyx which was thought to represent early cavitation.

It will be seen then that clinical information given by symptoms and x-ray findings can hardly be depended upon to give an accurate picture of the extent of the pathological process present in a tuberculous kidney. This lack of correlation between clinical information and pathological findings was constant throughout the whole series, regardless of the extent of renal damage. Kidney function tests of various kinds have been made but they have been found to have little value either in estimating the extent of the kidney damage or life expectancy.

The problem of innocent bacilluria. Almost every time discussion of renal tuberculosis takes place the question arises as to whether it is possible for a healthy kidney to excrete tubercle bacilli or if the finding of these organisms represents an actual destructive process in the kidney, which may heal, leaving no evidence of its previous existence. This is a very difficult question to answer but it may be said that none of the kidneys examined in this series showed small tuberculous lesions which could have been expected to behave in such a manner. All cases of purely miliary tuberculosis were excluded from the series.

In the entire group of 400 cases, tubercle bacilli have been cultured from the urine once in each of 10 patients in whom complete cystoscopic investigation and culture of ureteral specimens have failed to demonstrate any renal lesion. Five others have had one positive urine culture in a long series of negatives. The patients in this group have been regarded as suspects rather than cases of actual renal tuberculosis, because most of them had no symptoms. Tubercle bacilli were discovered in the routine urine examination of patients in the sanatorium taking treatment for some other form of tuberculosis. It has been the policy of this hospital to plant a T.B. culture of bladder urine from each patient at the time

of admission and repeat cultures are made when pus cells are present. In addition, urine cultures are made every 3 months in the case of patients suffering from forms of tuberculosis due to hematogenous spread, notably bone and joint cases. By means of these investigations it has been found that the incidence of genito-urinary tuberculosis in otherwise uncomplicated cases of pulmonary tuberculosis is about 3 per cent, while in the extrapulmonary group it is 23 per cent.

This routine culture of urine of sanatorium patients is analogous to the mass surveys which are being made of the general public by chest x-rays. It discovers renal tuberculosis in its early asymptomatic stage before the appearance of distressing tuberculous cystitis. In support of this statement is the fact that 27 (or 47.4 per cent) of the 57 patients who underwent nephrectomy had complained of no bladder symptoms whatever.

Indications for nephrectomy. As a result of the experience outlined above, it has become our custom to investigate as thoroughly as possible each case in which tubercle bacilli are demonstrated in the bladder urine by culture. This includes catheterization of the ureters and retrograde pyelography. If the ureteral specimen is positive and the pelvic outline shows cavitation, the kidney is removed even in the absence of bladder symptoms. If the pyelogram is normal a repeat cystoscopic examination is made and ureteral specimens are once more obtained for culture. If the second culture is positive for pus and acid fast bacilli nephrectomy is recommended. It is felt that this patient is suffering from clinical renal tuberculosis, with an ulcerative lesion in communication with the kidney pelvis in spite of a normal pyelogram.

A tuberculous pyonephrosis is removed if it is causing a fever even though there may be an earlier stage of tuberculosis in the opposite kidney. This is the only instance in which bilateral renal tuberculosis is operated on.

CONCLUSION

An outline of the pathological findings of the patients studied with renal tuberculosis is given.

No areas of healing were found in the surgical and autopsy kidneys examined.

Clinical renal tuberculosis is treated by nephrectomy as soon as a confirmed diagnosis is made even before pyelographic evidence of a cavity is found and before bladder symptoms occur.

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RENAL RICKETS AND POLYCYSTIC DISEASE OF THE KIDNEY[1]

HERMAN L. KRETSCHMER

The name "renal rickets" suggests the co-existence of renal disease and rachitic changes. The primary underlying disease of this syndrome is in the kidneys. Changes may be primary, such as interstitial nephritis, pyelonephritis, congenital polycystic disease, or hypoplasia of the kidneys. In some cases the kidney changes are secondary to lesions in the lower urinary tract, such as congenital valves in the prostatic urethra, stricture or stone, which lesions result in obstruction leading to bilateral hydronephrosis.

As a result of these various lesions, prolonged renal dysfunction ensues and is followed by rachitic changes. As a rule, these patients are seen late in the course of the disease when both the renal lesion and the rickets are well developed.

I wish to report the following case of bilateral polycystic disease of the kidneys which was followed by the development of rickets 3 years after the patient was first seen, in spite of the fact that he had been receiving cod liver oil in large doses, tomato juice and cereal since he was 3 weeks of age.

Unfortunately the child died at home in another city and only a partial autopsy was done. Hence it is impossible to state the condition of either the parathyroids, thyroid, or pituitary.

CASE HISTORY

J. P., a male infant aged 5 months, was admitted to Children's Memorial Hospital, September 23, 1935. Because of a cold the mother took the child to Dr. Foley of Waukegan 10 days before his admission to the hospital. On examination he found 2 palpable masses in the abdomen and an enlargement of the heart.

The child was born 17 days post-term. The labor was terminated by instruments after 10 hours of labor. The child was blue and was very difficult to resuscitate and he spent the first 4 days in an oxygen tent. The mother stated that the lungs did not expand, the child nursed poorly at the breast and did not gain weight until he was put on a formula. The mother stated that the child always had a big abdomen and that she had never seen blood in the urine. The child had been taking cod liver oil, tomato juice and cereal since 3 weeks of age.

The anterior fontanelle was open. The head was of good shape. The eyes, ears, and neck were negative. The throat was moderately injected. The lungs were negative. The aortic second sound was accentuated. In the left flank was a large hard mass, freely movable, which extended from the costal margin to below the anterior superior iliac spine. Mesially it extended to the left border of the left rectus muscle. A similar mass was present in the right flank which extended well into the pelvis. The retinal veins were engorged. The choroidal vessels were seen more distinctly than normal.

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 5, 1947.

Blood pressure on admission was 180/90.

The laboratory findings are summarized in tables 1, 2 and 3.

TABLE 1. *Urinalysis*

DATE	REACTION	ALBUMIN	SUGAR	BLOOD	SPECIFIC GRAVITY	MICROSCOPIC
9/24/35	Acid	0	0	0		No casts—no cells
10/1/35	Acid	0	0	0	1.008	1 cast seen
10/9/35	Acid	0	0	0		Rare R.B.C. seen
10/10/35	Acid	0	0	0		Occasional W.B.C. Rare R.B.C.
10/11/35	Acid	1+		+		Loaded with R.B.C.
10/16/35	Acid	Trace	0	0		6 to 8 W.B.C. low power field
10/24/35	Acid	0	0	0		No R.B.C.; 3 to 5 W.B.C.
3/10/36		Trace	0	0		Negative
7/8/38	Acid	Serum albumin 3 + nucleo albumin 0	0	0		R.B.C. none; W.B.C. every field
11/4/38	Acid	Serum albumin + nucleo albumin +	0	0		R.B.C. none; W.B.C. clumps

TABLE 2. *Blood chemistry*

DATE	N.P.N.	URIC ACID	CALCIUM	PHOSPHORUS	CREATININE	PHOSPHATASE
9/24/35	44.9	2.8				
9/26/35	41.3	3.5	10.9	5.2		
10/11/35	40.9	6.1			1.1	
10/19/35	42.3	3.4			1	
3/9/36	47.2	3.9			1.2	
3/11/36	41	3.6	11.2	5.4	1.1	
1/22/37	58.8	5.6			1.4	
8/8/38	80	5.7	9.5	5.3	1.6	26.63
11/4/38	48		11.8	5.23		26.42

TABLE 3. *Blood examinations*

DATE	HAEMOGLOBIN	R.B.C.	W.B.C.	POLYMORPHONUCLEARS	LYMPHOCYTES	MONOCYTES	EOSINOPHILS	BASOPHILS
9/23/35	80	5,320,000	14,000	36	58	6	0	0
3/9/36	90	5,320,000	11,200	29	66	2	2	1
11/22/36	80	5,250,000	33,600	19	76	4	1	0

X-ray examination by Dr. Anspach on September 24, 1935: Single view of the upper and lower extremities showed normal appearing bones. Anteroposterior and lateral views of the skull showed normal membranous bones and sutures.

Chest: There were possibly slightly accentuated densities in the region of the hila. No evidence of pulmonary disease.

Heart: Approximately 15 per cent enlarged in proportion to the size of the chest. The upper medial shadow was wide and made up of two degrees of density; could not rule out an enlarged thymus.

Abdomen: Single view of abdomen failed to show x-ray evidence of an abnormal density. The bones of the lower dorsal spine and pelvis appeared normal.

Intravenous pyelogram: No visualization of the urinary tract.

Preoperative diagnosis: Because of the enlargement of the heart, the accentuated aortic sound, the hypertension, the elevated nonprotein nitrogen, and the nonvisualization by intravenous urography, a preoperative diagnosis of bilateral polycystic kidney was made. After consultation with Dr. Brenneman and his staff, it was agreed that this patient should have the benefit of an exploratory operation, to rule out bilateral Wilms's tumor.

Operation (October 10, 1935, H. L. K.): Local anesthesia supplemented with a little ether. The usual kidney incision was made. The left kidney was enormously enlarged. It was paler than normal. The surface showed many indentations and was slightly irregular. On the surface were seen a few small cysts The pelvis was normal and there were no aberrant blood vessels. A piece was removed for histological study. The patient made an uneventful recovery. Discharged October 25, 1935.

Pathological report (W. G. Hibbs): Polycystic disease of the kidneys.

It is a well known fact that polycystic disease of the kidney has a tendency to run in families. Therefore special study was made of the family history which revealed the following: The father and mother were living and well and had no evidence of renal disease. One aunt (maternal) showed albumin in her urine when she was 13 years of age. The albuminuria persisted for 1 year; no further information was obtainable. One (paternal) great grandfather died of diabetes. One (maternal) great grandfather died of a stroke. One second cousin died of Bright's disease. One grandmother died of Bright's disease and high blood pressure. One aunt died at the age of 14 months of acute indigestion. This family history was significant. The question may well be asked whether or not his forebearers may not have had polycystic disease of the kidney.

The second admission was on March 9, 1936. The child was admitted to the hospital for purposes of study. He had had 2 attacks of vomiting. There was little change in his weight since his previous discharge from the hospital.

Head: Anterior fontanelle was open and slightly depressed. Eyes, nose, and mouth were negative. The pharynx was slightly injected. Few cervical glands were palpable, more marked on the right. Blood pressure 150/104.

The third admission was on September 14, 1936. The child was brought in for observation. Blood pressure 220/130.

The fourth admission was on January 22, 1937. The child was brought in for observation. There was some increased frequency of urination.

The fifth admission was on July 8, 1938. One and one-half years had elapsed since his last admission. The boy was now 3½ years old and was definitely dwarfed. He crawled instead of walking. The forehead was broad and glabella a little wide. There were enlargements at epiphyses of ankles and wrists with

lateral "bumps" and increased mobility. He continued to be irritable and at times seemed to have generalized discomfort. The veins on the forehead, trunk and flanks were prominent; costo-chondral beading 4 plus, rachitic in type; Harrison's groove; no change in size of the kidneys.

Examination on this date by Dr. Brenneman was as follows: "Child presents an extremely rachitic picture, is pale and has a rather large square head; sits in

FIG. 1

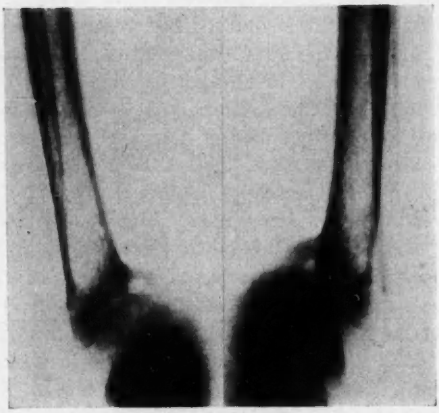

FIG. 2

tailor fashion with legs more or less bent as a result. He has a large stomach and small limbs. He has the most extreme rachitic rosary I have ever seen and the ends of the long bones are typically large. He has a marked Harrison's groove. The kidneys are easily palpable. Inasmuch as the child has been getting 3 teaspoons of cod liver oil daily since he was 3 weeks of age, I do not think that it is an ordinary rickets but a renal rickets."

It is to be noted that the rachitic changes developed during the 18 months that he was last seen in the Out-Patient Department.

X-ray examination on July 8, 1938: Anteroposterior views of both lower extremities and one upper extremity showed unusually marked thinning of the cortex and osteoporosis. There was a marked deformity through the metaphysis of the bones of the forearm and the bones of both legs just above the ankle.

The changes at the ankles and wrists were compatible with renal rickets but the changes at the site of the proliferating cartilage were not universal. However, there appeared to be some changes just distal to the epiphyses of the femoral head. The x-ray appearance was not that of infantile rickets. The bones of the skull showed some general loss of density but otherwise appear normal.

X-ray examination on November 4, 1938: Anteroposterior view of both lower extremities and one upper extremity showed the x-ray appearance little, if any, changed from that noted previously. The necks of the femora appeared nar-

FIG. 3

rower than previously and there was possibly some additional change in the contour of the right radius at the wrist.

See figures 1, 2, 3 and 4.

The child died at home June 22, 1939, at the age of 4 years and 2 months. Before his death he had great difficulty in breathing. Severe nausea and vomiting persisted for 1 week. The autopsy was limited to the abdomen.

Microscopic report: The kidney showed large cysts lined with flattened columnar epithelium. Many smaller cysts had ruptured walls. The section did not show glomeruli. There were, however, very few tubuli present which were not distended and cystic, or showed small lumina or none, because of frustrated regeneration. The stroma was dense, abundant and filled with round cells, especially around vessels.

The liver showed edema, the liver cells showed parenchymatous degeneration; the septa were hypertrophic and contained round cells. The bile ducts were distended.

Pathological diagnosis by E. Pribram: Polycystic kidneys, chronic hepatitis and edema of liver.

TERMINOLOGY

This syndrome has been variously designated as renal rickets, renal dwarfism, renal infantilism, renal hyperparathyroidism with osteoporosis, and osteonephropathy. It is understandable why such a diversity of terms have been employed. It is because a multiplicity of disorders have been found underlying the syndrome.

As more and more cases of this syndrome are being reported, many interesting speculations have arisen as to why the symptoms and pathological findings vary from case to case. All cases of renal rickets do not show uniform bone changes roentgenologically; all cases are not accompanied by dwarfism; all cases do not show parathyroid changes. In addition, it has been noted that the syndrome is not confined to childhood. Bone changes have been observed in adults with renal

FIG. 4

disease which some authors have considered the adult counterpart of the renal rickets occurring during childhood.

The co-existence of renal disease and bone changes were reported in the early literature, although the full significance of the relationship of the one to the other was not fully understood. Lucas (1883) was one of the earlier writers who called attention to the phenomenon of late rickets and albuminuria, and that they are too frequently connected to be matters of chance, and that the latter is often an important symptom indicating the cause of the former. Barber (1920) was the first to give the most accurate description of this syndrome and he called attention to cases of interstitial nephritis in children associated with stunted growth, some of them with infantilism in all its characteristics, others merely with a marked degree of dwarfism, and suggested the term "renal dwarfism" until a more suitable name could be found for this syndrome.

ETIOLOGY AND PATHOGENESIS

Why has there been so much confusion in the classification of cases of renal rickets? The understanding of the pathogenesis of this syndrome has increased in the last few years, but out of the multitude of theories presented, there still is no one hypothesis which completely explains the syndrome and much confusion exists. The chemical and physiological mechanisms involved raise many interesting questions. The principal theories presented have been the so-called renal, hyperparathyroid, pituitary-diencephalon, and recently the theory of acidosis.

Renal theory. As there is always present some form of advanced renal destruction, it is the generally accepted theory that the kidneys are the primary site of involvement in renal rickets. Most authorities are in accord that chronic kidney disease followed by skeletal changes, has led to the use of the term renal rickets. However, where authorities differ is *how* this renal dysfunction produces these skeletal changes and this has been the subject of many theoretical considerations.

Mitchell in his review of the literature offered his hypothesis as follows: ". . . In a type of nephritis characterized by a relative or absolute inability of the kidneys to excrete the waste endogenous phosphates from the body, there exists considerable evidence that such waste phosphates may be excreted through the intestinal mucosa instead of from the kidneys. It has been repeatedly demonstrated that an increased concentration of phosphates in the food, i.e., in the intestinal contents, may interfere with the absorption of calcium, presumably through the formation of insoluble calcium phosphates. An hypothesis offered is that in renal rickets such a shift of the excretion of endogenous phosphorus to the intestines occurs, and that the concentration of phosphorus in the intestine thus increased so blocks the absorption of calcium from the food that the child suffers a true calcium starvation with resulting bone changes."

The simple explanation of the lack of calcium absorption is not the whole story. This theory may explain the skeletal decalcification but it does not account for the presence of dwarfism or retarded sexual development seen in some cases, nor does it account for the cases in which the hypocalcemia is not pronounced. It also does not explain the cases of kidney disease with osseous changes which have come to autopsy and have shown changes in the parathyroid glands or in the pituitary gland.

This has resulted in the so-called parathyroid and pituitary theories to illustrate that the process of chemical imbalance is aggravated by endocrine disturbances, either in the parathyroids or pituitary gland, which gives the characteristic picture of renal rickets and which has borne different terms.

Parathyroid theory. The parathyroids have been suggested as being responsible for part of the pathological process because large parathyroids have been noted at postmortem in patients who died from renal rickets and chronic nephritis.

Some authors believe that the bone changes in renal rickets are the result of parathyroid changes and others even go further and state that it is one of primary

hyperexcretion of parathormone interfering with the calcium and phosphorus metabolism which produce microscopic calcifications and fibrosis in the kidneys, thus making the kidney condition a secondary one.

Shelling and Remsen state that the differentiation between primary hyperparathyroidism with renal damage and renal rickets depends upon the history of events which led to the combination of skeletal demineralization and renal impairment and upon the demonstration of an obstruction in the urinary tract. In renal rickets the renal impairment precedes the skeletal changes and there is usually a history of the presence of symptoms of renal disease and of stunting of growth long before the skeletal deformities become evident. In hyperparathyroidism, the changes in the skeleton antedate the renal symptoms.

Some authors are of the opinion that in primary hyperparathyroidism the blood calcium is high and phosphorus low, whereas in renal rickets it is the reverse. However, these criteria are not always reliable as a study of reported cases shows variations. F. K. Herbert, H. G. Miller and G. O. Richardson state that gross parathyroid hyperplasia is a rare complication of renal disease, but within the small group in which it is found, there is a high proportion of cases where the renal damage has been of long standing, and notably of congenital abnormalities of the kidney. They believe "that where renal disease is the primary abnormality the sequence of events is usually as follows: The renal failure leads to a rise in plasma phosphate. In response to the raised phosphate, the serum calcium falls. This is the common finding in the majority of cases of renal failure, and at this age of the process bony changes of the type of renal rickets or renal dwarfism may occur in young subjects. (The fact that bone disease may occur at a stage when parathyroid hyperplasia is absent is illustrated by the findings of Kluge. He examined 5 cases of renal dwarfism and renal rickets and found parathyroid hyperplasia in only one.) If the calcium deficiency lasts long enough it stimulates hyperplasia of the parathyroids and the hyperparathyroidism mobilizes calcium from the bones, either instituting osteitis fibrosa or aggravating previously existing bone disease. The serum calcium will be raised from the earlier low level to normal or even above it, but owing to the renal failure phosphate is still retained in the blood, causing oversaturation of blood and tissues with calcium phosphate and so giving rise to metastatic calcification." There is experimental evidence on record that renal insufficiency may give rise to parathyroid hyperplasia. Pappenheimer in 1936 removed portions of the kidneys in rats which resulted in hypertrophy of their parathyroid glands.

Although it is known that the parathyroid glands have a definite influence upon the calcium metabolism, the mechanism of this effect is still in dispute. Experiments carried on by Monahan and Freeman indicated that the parathyroid glands exert an influence on calcium metabolism that is independent of the kidneys. Albright stated that the primary action of the parathyroid hormone is on the phosphorus metabolism, and the changes in the metabolism of calcium are dependent on the preceding changes in the metabolism of phosphorus.

Ginzler and Jaffe state: "In some instances of chronic renal insufficiency the secondary parathyroid hyperplasia reaches such proportions as to leave no doubt that the total clinical picture has been complicated by the hyperfunctioning of

these glands. This hyperfunction, in turn, may instigate further damage to the kidneys and may also exert its influence on the osseous tissues, as in primary hyperparathyroidism. Indeed, the skeletal changes may even come to occupy the foreground of the clinical picture. Thus, in childhood, protracted renal insufficiency plus secondary hyperparathyroidism form the basis for the clinicopathologic picture somewhat inaccurately designated as 'renal rickets' ".

The authors go on to say that there have been cases of chronic renal insufficiency in adults in which the parathyroid hyperplasia was as pronounced as that associated with "renal rickets" and in which there were also very extensive osseous changes and that the skeletal changes occurring in the adult cases may be regarded as the adult counterpart of those occurring in "renal rickets" and, in both a condition of secondary hyperparathyroidism (due to the secondary parathyroid hyperplasia) is evidently partially responsible for the evolution of the osseous changes.

There is no doubt that the parathyroids do play a part in this clinical syndrome which accounts for the variations in the calcium and phosphorus blood levels seen from case to case, and the type of bone changes found, but its precise function is still difficult to evaluate.

Pituitary-diencephalon theory. In some cases a lesion of the pituitary gland was noted and the hypothesis was advanced that the clinical picture of this syndrome may be due to a pituitary-diencephalon lesion. Some of the characteristics of renal rickets have been difficult to explain, e.g., the dwarfing, the infantilism, the polyuria. A pituitary lesion might explain the dwarfism and infantilism, for both growth-producing factors and the sex-stimulating factors are centered in this gland.

Roberts reported a case with atrophy of the pituitary which showed dilatation of the urinary tract without "apparent obstruction." Ellis and Evans reported 20 cases of renal rickets which had marked dilatation of bladder and ureters without "obvious obstruction." Attention should be called to the fact that the cause of marked dilatation of bladder and ureters in children is so frequently due to valves in the prostatic urethra which are overlooked because special search is not made for them. Routine removal of the prostatic urethra in children is rarely carried out, hence it is possible that the presence of valves in cases is so very easily overlooked.

Harris in his book on bone growth indicates that the clinical picture of renal rickets can best be explained by a pituitary diencephalon lesion. Firestone states that the retardation in the appearance of the secondary sexual characteristics is probably due to a secondary involvement of the pituitary gland, which in turn acts on the gonads. Charnock also explains it on the pituitary-diencephalic theory and states that pituitary dysfunction could cause the dwarfism, and that, secondly, an autonomic center in the adjoining diencephalon could cause urinary tract abnormalities in which there is no mechanical block. As stated by Charnock: "It is altogether likely that an overlap in these theories may occur and that the initial lesion may be found in the pituitary diencephalon area which results in urinary tract disorders, thus allowing the chemical imbalance of calcium and phosphorus metabolism to finally result in a secondary parathyroid hyperplasia."

Chown and Lee are supporters of the pituitary-diencephalon theory. Although there is not sufficient evidence to support this theory wholeheartedly, it does suggest an avenue for future investigation of certain manifestations which appear in the renal ricket syndrome. I wish again to call attention in presenting these theories that in my case the primary lesion was in the kidney and the rickets did not develop until 3½ years later.

Acidosis. At the present time there has been a tendency to explain this syndrome on the basis of acidosis. Ginzler and Jaffe believe that chronic acidosis resulting directly from renal insufficiency plays the important role. These authors stress the fact that osseous lesions of a much milder type can almost regularly be found in adult cases of prolonged renal insufficiency; that these bone changes may be associated with only mild or moderate parathyroid hyperplasia and even, rarely with no gross or microscopic parathyroid hyperplasia, so that it seems plausible to them to explain their development on another basis than secondary hyperparathyroidism.

This viewpoint is also supported by Rutishauser and co-workers who published several papers between 1935 and 1938, and who called attention to the regular occurrence of osseous changes in adults with chronic renal insufficiency as well as in animals with experimentally produced renal insufficiency. They too question the role of the parathyroids in the genesis of those mild changes and stress the importance of the acidosis which is constantly present.

I. Snapper states that the renal failure must be of long duration and that the renal failure must give rise to acidosis. He believes that if the renal failure is accompanied by acidosis of exceptionally long duration, the hyperplasia of the parathyroids may lead to the formation of tumors of a considerable size. Skeletal changes may develop at the same time. He goes on to say that there is no conclusive evidence that the parathyroid hyperplasia occurring in uremia is caused by the increase of the blood phosphate and states that as far as the causation of the osteodystrophy in chronic uremia is concerned, experience in North China has shown that the bone lesions develop in patients with acidosis but without chronic hyperphosphatemia.

SYMPTOMATOLOGY

The disease occurs in childhood and early adulthood. Both sexes are equally affected. The outstanding symptoms are failure to grow, bony deformities, such as knock-knee, enlargement of epiphyses and costochondral junctions, presence of Harrison's groove, rachitic rosary, and bowing of the tibia, difficulty in walking, increasing weakness, polydypsia, polyuria and symptoms of uremia, and evidence of delayed sexual development. There may be cardiac enlargement. Secondary anemia is usually present. There is marked dryness of the skin and a yellow-brown pigmentation. In the terminal state, occasionally hypertension with arteriosclerosis is present. Mitchell in 1930 mentions the frequency of sclerosis, thickening and atheromatous patches in the aorta and other blood vessels. Arterial calcification in renal rickets has been noted by Smyth and Goldman, Shelling and Remsen, Baggenstoss and Keith, and Hild reported on calcification of arteries and deposits of calcium in both lungs. Kidney function

tests will show impairment of renal function. The blood phosphorus is nearly always elevated which is believed to be due to the inability of the kidneys to excrete the waste endogenous phosphates. The blood calcium may be low, normal, or even increased. Urine examination will reveal almost always a low specific gravity and albumin; at times, casts and white and red blood cells. Most cases terminate in uremia.

However, no 2 cases are alike and as Howard stated "this is a disease of contradictions."

SUMMARY AND CONCLUSIONS

A case of renal rickets is presented. The renal lesion was congenital bilateral polycystic disease. Rickets developed in spite of the fact that the child had been taking cod liver oil, tomato juice and cereal since he was 3 weeks of age. The patient presented an extremely rachitic picture, namely, extreme rachitic rosary, typically large ends of the long bones, and marked Harrison's groove. The marked rachitic changes developed between two admissions to the hospital, a period of 18 months. The blood calcium and blood phosphorus were always within normal limits. The blood phosphatase was 26.63 mg. per cent. It is to be remembered that in this patient the first and primary lesion was renal. Whatever other changes occurred are secondary.

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DISCUSSION

Dr. Reed M. Nesbit (Ann Arbor, Mich.): I would like to ask Dr. Keyser if he has seen any evidence of injury to the ureter from prolonged use of indwelling ureter catheters.

Dr. Archie L. Dean (New York, N. Y.): I should like to ask Dr. Keyser what strength of urease solution he uses preliminary to irrigating with Suby's solution.

I should like to express my appreciation of Dr. McClelland's paper, and suggest that it may be a good basis from which to study results with streptomycin in renal tuberculosis. We are doing that now in one of the Veterans' hospitals, with most encouraging early results, and I believe the use of streptomycin may change the outlook regarding healing of early tuberculous lesions in the kidney.

Dr. George R. Livermore (Memphis, Tenn.): I would like to ask Dr. Keyser about the irritation produced by this irrigation in the bladder.

Dr. Ben D. Massey (Pasadena, Cal.): I should like to ask Dr. Keyser if they have had to use any apparatus for introducing a mild positive pressure for extending of the renal pelvis to get at the stones and calyces.

Dr. Linwood D. Keyser (Roanoke, Va.): Dr. Nesbit has mentioned the possibility of traumatic necrosis of the ureter from prolonged use of indwelling catheters. He is quite correct. Shaw and others have reported cases of ureteral necrosis under such conditions and this is one of the hazards of any type of prolonged ureteral drainage.

Dr. Keyes: Have you had any trouble?

Dr. Keyser: Yes, I have, but not of this type. As we all know, there is a tremendous individual variation in the ability of patients to tolerate indwelling catheters even for a short time. Certain people possess particularly spastic ureters, so that when even a small ureteral catheter is introduced atraumatically and without fluid injection, the urine, at first clear, becomes bloody after an hour or two if the catheter is left in place and there is excruciating pain. Such cases are exceptional and are found more often in patients who have reno-ureteric colic without stone or organic obstruction, than in those with this latter type of disease.

A prerequisite of the effort at retrograde disolution of stone is, therefore, the ability of the patient to tolerate indwelling catheters without severe pain, hematuria, or febrile reaction. I usually start by dilating the ureter under pentothal or low spinal anesthesia with bougies up to 10 or 11 F. The three No. 5 F. catheters then can, as a rule, be inserted fairly easily. Persistent pain, fever or gross hematuria must be absent before the irrigator is attached. If present, remove the catheters, wait until untoward reaction has subsided and perhaps make another trial after a rest period of a week. During the period patients are on the irrigator, penicillin, streptomycin and at times sulfa drugs adapted to the bacteriologic findings are administered daily.

Dr. Dean has asked of the preparation of the ferments, especially urease. We

use a 0.5 per cent suspension in sterile saline. The ferment itself cannot be sterilized without impairing its efficiency, so we weigh out the ferment from the container which the manufacturer gives us, using sterile apparatus. We admit another hazard here. Each suspension is cultured and usually we find only saphrophytes present. If staphylococci or streptococci are found, we discard this batch and make up another. To date, we have not been aware of any urinary infection introduced in this manner, but admittedly it might happen.

Dr. Livermore has asked about the irritation produced by these solutions. The ferment suspensions with the possible exception of ficin proteinase are non-irritating. Ficin must be handled with care and at times I start with a 0.25 per cent suspension. I have had 2 cases of slight hematuria and pain from irrigation with 0.5 per cent ficin, which quickly subsided after its discontinuance. As for the citrate solution, Albright's original acid sodium citrate was irritating at times. Suby in developing G and M solutions added magnesium probably for two reasons, viz., magnesium lessened the irritability of the sodium acid citrate and also it seemed to form a complex magnesium calcium ion. This avidity of magnesium for calcium intensifies the solvent effect of G solution above and beyond its hydrogen ion effect.

Clinically irritation from G solution has been minimal both in the renal pelvis and in the bladder. Occasionally pain and fever are indications for discontinuing irrigation for a few days. However, not infrequently we are able to keep irrigation going for as long as 10 days with little or no reaction. In one instance, the patient had a temperature of 102° F. 3 days after all the irrigation apparatus had been removed. This reaction was speedily brought under control by antibiotics.

Dr. Massey has brought up the question of use of pressure in the irrigating apparatus in order to keep the pelvis and calyces filled with irrigating fluid. Suby and Albright have emphasized this feature of retrograde dissolution technique and have devised their apparatus accordingly.

With the 3 catheter system, I have used weak solutions of skiodan and find that while the irrigation is in progress, a fairly well-outlined pyelogram may be obtained by x-ray. Filling the kidney under pressure, I feel, endangers overdistension and possible pyelovenous backflow. This is a point yet to be determined. In short, the whole program of retrograde calculus dissolution is decidedly in the developmental stage. Each of us working in the field awaits eagerly new contributions which may give hope for a more practical scientific approach to the problem.

Dr. James C. McClelland (Toronto, Ontario): Most of our patients, these very early ones, have been treated previous to the use of streptomycin. We have had it in mind, but it is very expensive to get, and the results have not been conclusive, so we haven't felt that it was justifiable to use it. A lot of drug has to be used, and over a long period of time, but we have it in mind, and we will try it as soon as we can see that there is an indication for it.

Dr. Herman L. Kretschmer (Chicago, Ill.): Dr. McClelland brought up the question of the tubercle bacilluria. That is always a debatable point and has

always caused a good deal of discussion. There are many who believe that when tubercle bacilli pass that the patient has organic disease, even if you can't prove it. I had an interesting experience with this problem some time ago in which a patient had tuberculosis of both ankles and one wrist and in the tendons of his opposite hand. He also had tuberculosis of both epididymes. Studies of the urine showed tubercle bacilli, but no pus. This was in the days before intravenous urograms, so two sets or retrograde pyelograms were made. Three sets of guinea pig inoculations were made, and three sets of smears, which showed bacilli in the bladder, urine and bacilli in the right kidney.

In view of the fact that there was no evidence of bladder tuberculosis and no pus in the urine, and because the pyelogram was normal, a good deal of discussion was given to the fact that this patient probably had a true case of tuberculous bacilluria. I operated upon that patient. Dr. Keyes was there that day. There was a good deal of doubt in my mind whether we should take the kidney out, because the kidney appeared normal. Dr. Keyes said: "I always get a great deal of help from the ureter." I pulled the ureter out, and it was normal. I took that kidney out, and the kidney was normal, but on the posterior wall of the pelvis was a large, tuberculous ulcer from which the bacilli apparently came into his urinary stream and were found by guinea pig inoculation.

I think if it were possible to have more cases of that type where you can verify the fact that the patient with tuberculous bacilluria, so-called, without pyeluria usually has an organic lesion somewhere in his urinary tract, it helps.

DISAPPEARANCE OF CARCINOMATOUS ULCERATION OF BLADDER FOLLOWING URETEROSIGMOIDOSTOMY: REPORT OF 2 CASES

EDWIN DAVIS

"Nothing's so hard but search will find it out."
—Robert Herrick

It is my purpose to report the clinical disappearance of carcinomatous ulceration of the bladder following diversion of the urinary stream, and to point out the possible biological significance of this phenomenon in connection with the etiology of certain bladder tumors. These observations are based upon repeated cystoscopic studies, confirmed by preoperative biopsy, and by subsequent gross and microscopic examination of the excised bladder by competent pathologists.[1]

The obvious inference that these tumors were caused by a carcinogenic urinary ingredient is thought-provoking, and involves a consideration of the closely related subject of chemical carcinogenesis, which may be defined as "the production of malignant, transplantable, metastasizing new growths, in laboratory animals or human beings, by the action of cancer-producing chemicals introduced into the body, intentionally or inadvertently, by ingestion, inhalation, injection, or cutaneous application" (Davis[2]).

Although having received but scant mention in other than special journals, the experimental achievements in this field during the past 15 years have been but little short of astounding. "Cancer may be produced at will in a majority of the animals treated, with a variety of chemical compounds" (Cook[3]), mostly prepared synthetically, and of known molecular structure. Proven carcinogenic substances are exceedingly numerous and varied as to chemical structure, and may be naturally occurring or synthetic, organic or inorganic, exogenous or endogenous in origin. There is evidence that carcinogens may masquerade unrecognized as innocent substances, resulting in chronic occupational, environmental, therapeutic or cosmetic contact. There is proof of the carcinogenic potency of certain artificial ingredients of foodstuffs (Cook and Kennaway,[4] Reding[5]), and evidence has even been submitted directing suspicion against certain foodstuffs themselves, among these glucose, sesame oil (Schiller[6]), wheat

[1] Drs. J. P. Tollman, Prof. of Clin. Path., and H. E. Eggers, Chairman Dept. Path. and Bact., Univ. of Nebr. Coll. of Med.

[2] Davis, Edwin: Chemical carcinogenesis, drugs, dyes, remedies and cosmetics with particular reference to bladder tumors. J. Urol., **49:** 14, 1943.

[3] Cook, J. W.: Carcinogenic chemical agents. Yale J. Biol. and Chem., **11:** 1, 1938.

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[5] Reding, R.: Des Dangers de Cancerization Resultant de L'emploi de Colorants Dans L'almentation et en Therapeutique. Acta, **4:** 734, 1939.

[6] Schiller, W.: Rat sarcoma produced by the injection of the dye, light green F.S. Am. J. Cancer, **31:** 486, 1937.

germ oil (Rowntree et al.[7], Rider[8]), olive oil and lard (Burrows et al.[9]). Steiner et al.[10] after an extensive investigation as to "the possible carcinogenicity of over-cooked meats," and other substances, advised "further study of the carcinogenic potency of heated vegetable fats." Awaiting confirmation is the report (Widmark[11]) of carcinogenic substances obtained from roasted meat and browned butter. Eller and Wolff,[12] reviewing the literature, concluded that "the evidence that experimental tumors can be produced by a diet rich in vitamins is inconclusive," although stating that the majority of authors consider vitamin excess to be a factor in tumor initiation and tumor growth.

In addition to these multiple exogenous sources, carcinogenic properties have also been ascribed to certain endogenous (physiological) substances produced within the body, among these acetylcholin and estrogens. For instance, Hall and Frank[13] reported "an inordinate number of tumors which developed in various animals" during prolonged acetylcholin administration. Cramer[14] considered the carcinogenic potency of estrogenic substances, in producing mammary cancer in mice, discovered by Lacassagne,[15] to be "based upon evidence which is incontrovertible." Eller and Wolff, reporting a certain commercial estradiol-containing face cream which "produced cancer in animals, as well as other profound systemic changes, when applied on the skin in one-fifth the amount recommended for daily use by women," have quoted numerous warnings from authoritative sources against indiscriminate, prolonged use of estrogen-containing ointments. The chemical grouping known as the phenanthrene nucleus, possessed in common by the most potent of the carcinogenic hydrocarbons, is "widely distributed in nature in a variety of physiologically important compounds, including cholesterol, vitamin D, the bile acids and the sex hormones." (White[16]) Auchincloss and Haagensen[17] have commented upon the unrestricted and promiscuous use of estrogenic substances in cosmetics. Moreover, this topic has been considered of sufficient importance to have appeared in the editorial columns of the *Journal of the American Medical Association*,[18] where a

[7] Rowntree, L. G., Steinberg, A., Dorrance, G. M., and Ciccone, E. F.: Sarcoma in rats from the ingestion of a crude wheat germ oil made by ether extraction. Am. J. Cancer, **31:** 359, 1937.

[8] Rider, Dean L.: An experiment in feeding wheat germ oil prepared by ether extraction. Am. J. Cancer, **38:** 275, 1940.

[9] Burrows, H., Hieger, I. and Kennaway, E. L.: Experiments in carcinogenesis: The effect of the subcutaneous and intraperitoneal injection of lard, olive oil and other fatty materials in rats and mice. J. Path. and Bact., **43:** 419, 1936.

[10] Steiner, P. E., Steele, R. and Koch, F. C.: The possible carcinogenicity of overcooked meats, heated cholesterol, acrolein, and heated sesame oil. Cancer Research, **3:** 100, 1943.

[11] Widmark, E. M. P.: Abstr. Science N. L., **35:** 388, 1939.

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[13] Hall, G. E. and Franks, W. R.: Physiological carcinogenesis. J. Biol. Chem., **123:** XLIX-L (Scientific Proceedings), 1938.

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[16] White, A.: Carcinogenic substances. J. Connecticut Med. Soc., **3:** 4, 1939.

[17] Auchincloss, H. and Haagensen, C. D.: Cancer of the breast, possibly induced by estrogenic substances. J. A. M. A., **114:** 1517, 1940.

[18] Editorial: Contraindications to estrogen therapy. J. A. M. A., **114:** 1560, 1940.

distinct note of warning has been sounded. Supporting the work of Steiner,[19] who demonstrated the sporadic occurrence of carcinogenic substances in human liver (20 per cent of specimens examined), Hieger[20] has very recently reported "a sarcoma-producing fraction—obtained from mixed lung-kidney-muscle of cancerous and non-cancerous human (autopsy) subjects."

The above array of seemingly irrelevant and unrelated facts, indicating the multiplicity, variety and ubiquity of carcinogenic substances, is submitted by way of evidence that the idea of a carcinogen as an ingredient of human urine, either exogenous or endogenous in origin, is by no means fantastic, and has, in fact, ample precedent. The so-called "anilin" bladder tumor of dye factory workers, long recognized, its identity and etiology established beyond question, serves as a classical example of a new growth due to a carcinogen of exogenous origin, inadvertently assimulated in infinitesimal daily dosage, through a long period of years, by ingestion, inhalation or inunction. The brilliant achievement of Hueper[21] and co-workers, who succeeded in the production of bladder tumors in dogs by feeding beta-naphthylamine (one of the "intermediates" in the synthesis of anilin dyes) has afforded incontrovertible experimental proof substantiating the mass of clinical evidence concerning the etiology of these tumors. The amazing feature is that "anilin" tumors should be produced in an organ remotely removed from the point of contact with the carcinogen, and not elsewhere in the body except in the urinary tract. Concerning the two schools of thought as to whether the contact of the carcinogen (or its "organic conversion products") with the bladder epithelium is via the urine or the blood stream, Hueper[22] has cited evidence whereby "the majority of investigators" favor the urogenous route. This opinion is in keeping with the known characteristics of bladder tumors, and with the evidence herein presented.

The strange "habits" of bladder tumors, characterized by a strong tendency to multiplicity and repeated reappearance (as distinguished from recurrence) *elsewhere* in the bladder following transurethral destruction are familiar to all. It was reflection upon this unconventional behavior of bladder papillomata, together with the extraordinary and intriguing facts in connection with anilin bladder tumors, suggesting a urine-borne carcinogen, which stimulated my interest in chemical carcinogenesis. As long ago as 1942, I presented before the American Urological Association[2] a review of achievements in this field, together with evidence justifying the hypothesis that the genesis of certain "spontaneous" bladder tumors might bear a relationship to unrecognized carcinogens masquerading as innocent substances and encountered through environmental or occupational contact, or included among the endless list of drugs, remedies,

[19] Steiner, P. E.: The induction of tumors with extracts from human livers and human cancers. Cancer Research, **2**: 425, 1942.

[20] Hieger, Izrael: Carcinogenic substances in human tissues. Cancer Research, **6**: 657, 1946.

[21] Hueper, W. C., Wiley, F. H. and Wolfe, H. D.: Experimental production of bladder tumors in dogs by administration of beta-naphthylamine. J. Indus. Hyg. and Tex., **20**: 46, 1938.

[22] Hueper, W. C.: Anilin tumors of the bladder. Arch. Path., **25**: 856, 1938.

cosmetic concoctions, synthetic vitamins and sex hormones, and the countless anilin dyes used in the coloring of food stuffs and fabrics.

In the discussion following the presentation of this paper Dr. Robin Pearse[23] of Toronto, at my insistent request, reported "2 cases of marked regression of infiltrating papillary carcinoma of the bladder occurring after the bladder had been at rest." Although it is not clear whether it was his purpose to emphasize the resting bladder or the absence of urine as the causative factor, and although preoperative biopsy confirmation was lacking, the evidence submitted by Dr. Pearse of the relationship between ureterosigmoidostomy and "regression" of the tumor is to be viewed as impressive.

It was a consideration of these pertinent and intriguing facts which prompted speculation as to what might have occurred as the result of diversion of the urinary stream, and led to cystoscopic examination in the first case, after a 50 day interval following ureterosigmoidostomy.

CASE REPORTS

My own 2 "phantom" tumor observations were so essentially similar as to render separate detailed case reports unnecessary. The patients were both male, aged 56 and 60 respectively, each complaining of hematuria without other symptoms or physical findings of significance. In neither case was the tumor to be made out by combined rectal and abdominal palpation under spinal anesthesia.

Preoperative cystoscopic examination in the first case showed a rounded, crater-like ulceration, about 2 cm. in diameter, with an elevated edge, situated just behind the trigone and to the left of the midline. In the second case it was not possible to distinguish positively, by cystoscopic inspection alone, between inflammation and new growth. This lesion, situated on the left lateral bladder wall, 2½ cm. in diameter, and slightly elevated, showed an edematous-looking, reddened surface, but no actual ulceration, and no papillary processes. Bladder elsewhere was normal in each case.

Preoperative biopsy specimens, removed with the resectoscope, in each instance were reported carcinoma. In the second case Drs. Tollman and Eggers[1] concurred in the opinion that the histological picture was that of a highly malignant type of carcinoma.

Bilateral ureterosigmoidostomy in each instance was uneventful, both with respect to technique and convalescence.

Postoperative cystoscopic inspection, carried out both by my associate, Dr. Lee, and myself, under caudal anesthesia, with excellent illumination and excellent cooperation upon the part of the patient, after 50 day and 71 day postoperative intervals respectively, showed the bladder mucosa beautifully normal throughout, and without any indication whatever that these were the same bladders previously visualized.

Postoperative biopsy, performed upon case 1 only, by removal with the resectoscope loop of a deep bite of tissue through the normal mucosa at the site

[23] Pearse, Robin: Discussion following paper by Davis, Edwin. J. Urol., 49: 14, 1943.

of the previous ulceration showed cancer cells situated in the underlying muscle tissue.

Cystectomy, under continuous spinal anesthesia, in each instance was uneventful, as was convalescence.

The *pathological reports* likewise were strikingly similar. In each case careful gross inspection of the excised bladder showed no evidence of intravesical new growth, or extravesical extention. See figure 1. Microscopic section of the bladder wall, however, in each case showed cancer cells in the tissues underlying the normal mucosa.

In case 1, as reported by Dr. Tollman, "section of the wall of the bladder showed massive invasion by tumor, which in most places appeared as large un-

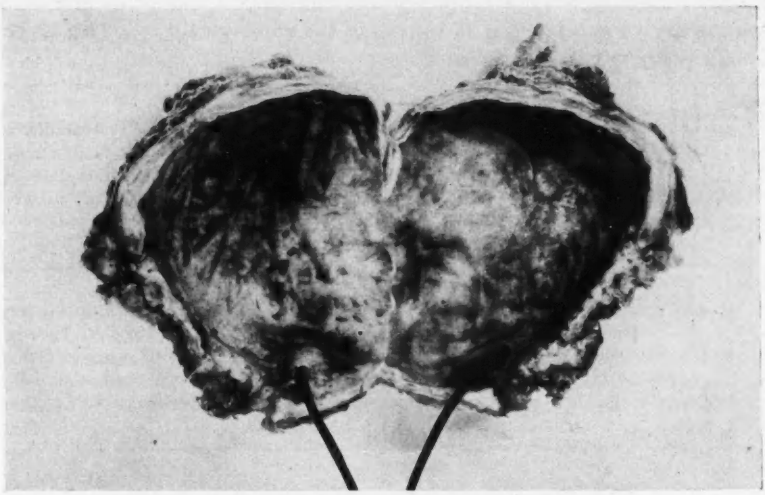

FIG. 1. Case 2. Sagittal section of cystectomy specimen

organized masses of cells, with small areas at intervals showing quite distinct glandular formation. Diagnosis, adenocarcinoma of bladder."

In case 2 "sections were taken at several points including the full thickness of the bladder wall. One of these sections showed residual tumor cells similar to those in the earlier biopsy specimen. Diagnosis, papillary carcinoma of bladder."

In response to *follow-up inquiry* each patient reported himself symptom-free at the end of 3 and 14 postoperative months respectively.

COMMENT

It is to be clearly understood that it is not my purpose to advocate ureterosigmoidostomy as a therapeutic or curative measure, but rather to direct attention to the possible biological significance of this phenomenon. It is true, however, that in cases of bladder tumor not amenable to recognized methods

of treatment, diversion of the urinary stream may provide a very gratifying degree of symptomatic relief, and, incidentally, an opportunity for observation and accumulation of data, and, to this end, cystoscopic examination following ureterosigmoidostomy is urged.

Since ample experimental and clinical evidence has been cited to provide precedent for the presence of a carcinogen (exogenous or endogenous in origin) as an ingredient of human urine, it is to be hoped that interest stimulated by these observations may further our knowledge concerning the etiology of certain bladder tumors. The fact that cancer cells were shown to persist in the deeper tissues does not detract from the biological significance of the complete disappearance of the intravesical portion of the tumors. In the event that the inference concerning a urine-borne carcinogen is correct, the possibility of confirmation by the development of tumors of the rectosigmoid following ureterosigmoidostomy is to be anticipated.

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COMPARISON OF THE MALIGNANCY OF BLADDER TUMORS AS SHOWN BY THE CYSTOSCOPIC BIOPSY AND SUBSEQUENT EXAMINATION OF THE ENTIRE EXCISED ORGAN[1]

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The purpose of this paper is to record frequent discrepancies in the diagnosis of bladder tumors based on examinations of the cystoscopic biopsy and the entire excised organ. The clinical material studied consisted of 100 consecutive patients with bladder tumors treated by diversion of the urinary stream and cystectomy.

TABLE 1

	cases
Examination of the entire bladder showed tumor to be of the same grade of malignancy as that found in cystoscopic biopsy	42
Cystoscopic biopsy showed tumor of higher grade of malignancy	4
Examination of entire bladder showed tumor of higher grade of malignancy	50

TABLE 2

	cases
Several cystoscopic biopsies were performed. Examination of bladder showed a degree of malignancy less than that of at least one cystoscopic specimen	1
Several cystoscopic biopsies were performed. Examination of bladder showed a degree of malignancy greater than that of at least one cystoscopic specimen	3
Total number of discrepancies between pre- and postoperative pathological examinations	58

TABLE 3

Examination of excised bladder showed previously unrecognized tumor infiltration beyond that organ in at least 9 patients. They had been studied before cystectomy by cystoscopy, roentgenography, bimanual palpation while anesthetized and visually and by direct palpation when the ureters were transplanted.

Tables 1 and 2 show that in 58 of 100 cases the microscopic examinations of the entire bladder differed from those made on specimens removed through the cystoscope. Of much greater clinical significance is the fact that in at least one-half of all patients operated upon the true condition was of a greater degree of malignancy than the cystoscopic biopsy had indicated. While the grading of bladder tumors is but one of several important diagnostic measures it does indicate with considerable accuracy certain features of the natural history of the growth which the clinician must recognize in choosing appropriate therapy. When treatment as radical as diversion of the urinary stream and cystectomy is

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 6, 1947.

contemplated there should be reasonable assurance that after surviving removal of the entire bladder and prostate the patient will be completely rid of his disease. Unfortunately, as is evident from our experience, preoperative pathological examinations frequently have provided such misleading data that the true nature of the growth remains uncertain. In a considerably smaller but still substantial proportion of cases even direct observation and palpation of the exposed bladder has failed to demonstrate the full extent of the disease. Until such a time, therefore, when more exact examinations have been devised successful treatment of bladder tumors depends, as it always had depended, on mature clinical judgment.

30 E. 40th St., New York 16, N.Y.

EPITHELIAL BLADDER TUMORS ATTACKED BY RADONS AND FULGURATION DURING THE YEARS, 1926–1938[1]

EDWARD L. KEYES

There was, you might say, no treatment for bladder tumors until Beer gave us fulguration, and metal radons followed in 1926 to provide the first decent treatment for such tumors as did not respond to fulguration.

So I begin this record in 1926 and close it 8 years later, when I was shut off from surgery.

Our experience with the electronic attack on bladder tumors at Memorial Hospital had been horrible. Radium bombs and glass radons left so small a margin between the therapeutic and the mortal dose that many a patient who took 4 years to die in agony of radium burn, died with cancer uncontrolled.

My first experience of the healing power of radium was when, in 1919, I returned from the war and to an old woman whom I had left in Dr. Barringer's hands with a bladder full of papillary tumors that my fulgurations had failed to weed out. He had put a radium bomb in her bladder and 16 months later, when I saw her she was still complaining of bladder spasms but then and for the 7 years after treatment that I followed her, she seemed free of tumor.

A few happenings like this made me so cocky that when a Manitoba doctor wrote me about a patient with a desperate bladder tumor, I answered that, if tumor and patient were movable, he might send them to New York. On the way down Dr. MacKenzie saw her and made no promises but was polite about it.

This tumor proved to be single, sizable and well up on the lateral wall. It was reported as cancer, glass radons were implanted and she had spasms for 2 years, but remained well for ten.

At the Memorial Hospital I also learned how promptly tumors recur after partial cystectomy and was taught to have no trust in x-ray therapy.

THE FIRST FIVE YEARS

This is a report of what little I know about the fate of 111 patients treated by electronics during the last 8 years of my professional life (table 1). Treatment of some of them had been begun previously. In fact, one of the most annoying of the characteristics of these patients is that they drift away and, one never knows whether to assess them as controlled or uncontrolled.

These 111 patients were treated by electronics. There is no mention here of cystectomy, thermocauterization, x-ray therapy or even of the liq. hydrargyri nitratis of which one application wiped out the urethral tumors of 1 case. Indeed, urethral tumors are not mentioned and one man whose bladder tumors were controlled by a single radon implantation is not listed because he died of his urethral tumors, which I was too young to know how to control.

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 6, 1947.

Also, in order to make this a purely tumor record, the prostate, the arteries, etc., are out of it. Death by urosepsis is attributed to cancer or to radon burn, I think fairly. Indeed, after the first 5 years, there seems no profit in recording the 3 cancer deaths I know of or the deaths by intercurrent disease. These are but unhandy interruptions to the clinical history.

I have resisted the temptation to expand on the subject of spontaneous cure for I am aware that—well, I have found no spontaneous cures among my cases.

TABLE I.

111 patients:
- 36 died within 5 years of onset;
  - 29 of cancer (or were due to die when last heard from),
  - 2 of intercurrent disease,
  - 2 postoperative (51 suprapubic sections on 46 patients),
  - 3 of radon burn (large reimplantations within 2 years),
- 26 not in failing health, disappeared.
- 49 followed 5 years (7 of them inadequately described or too briefly or feebly treated to be noteworthy so—to the 42 survivors—this paper is devoted).

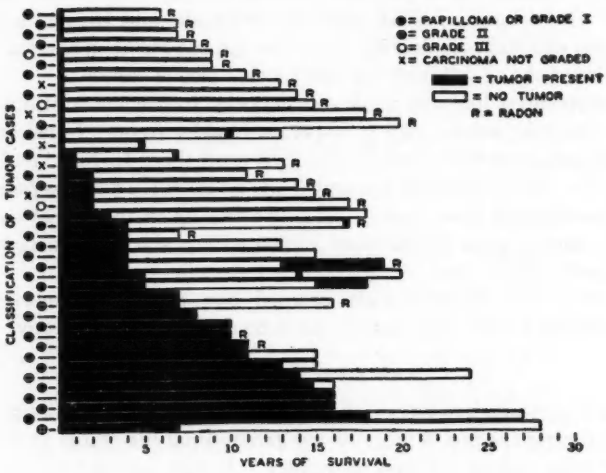

FIG. 1

In short, within 5 years about 1 patient in 3 died of cancer, almost as many got bored with me and fled, I killed 1 in 10 of the patients I opened. I have a good record 5 years after onset of more than 4 out of 10 bladder tumor patients. For the care of these patients after 1934, and for the addition of the resectoscope to our armament I have to thank Dr. Allister M. McLellan.

THE FIVE YEAR SURVIVORS

At the bottom of the chart shown in figure 1 the duration of tumors and their recurrences is entered in black. The innumerable (but of ill-defined duration) intervals of less than 5 years are not noted, neither are the many terminal nega-

tive cystoscopies. Why bother? It takes more time than we have observed any of these recurrent tumors to be confident that the worst is over. Our most conscientious patient had 2 Percy operations and a lot of fulgurations and one radon implantation in the first 4 years. Then for 9 years a negative cystoscopy annually, then a cancer recurrence and, in spite of all the radons Dr. Nesbit could stuff into her, a frozen pelvis and she died.

But let us get back to our chart (fig. 1). The case at the very bottom just got in by a few fulgurations in 1926. The topmost recurrent case was treated only by fulguration. There is one other, a cancer, that did better but is not here. I fulgurated once in 1916, Dr. Hepburn could find no tumor in 1923, the patient is well today (31 years).

The last treatment given all the other recurring tumors, except those marked R, was fulguration with the wire or the loop. One has to learn how to use the resectoscope in the half empty bladder. It is like learning to drive a car: you need an accident to make you competent.

Our most effective treatment has been to open the bladder and implant radons, of 1.5 mc. strength, never more than 30 in number and, on the average, 10. Small growths, not too numerous, were planted with a few radons by cystoscope. Note how the best cases are all marked R (radon) as the decisive element in their cure. Recurrences represent radon failures, notably the 3 cancer deaths who got, all of them, a shot of radons as a last (and vain) hope.

Many of the successful cases had 2 or more radon shots by cystoscope; only 1 was controlled by a second suprapubic implantation: (20 radons the first time; 2 year interval; 13 radons; no burn; well 13 years when he died by a coronary occlusion after prostatic resection.)

Note especially the character of the tumors that recurred the longest; 8 out of 10 of them were papillomata or grade 1. The grade 3 tumors seemed more controllable than the grade 2. Today your stronger electrical power and your psychological employment of anesthesia give you a better hold on tumors.

Look at the grade 3 tumors. Supposing all the patients who died in the first 5 years were grade 3, we have 29 of these against 3 who survived and recurred no further.

THE MOST EXTENSIVE TUMOR THAT WAS CONTROLLED

Here is an extract from the operation record of our most extensive tumor. Two years after onset the tumor was grade 2 and bimanually palpable before anesthesia. The operation was performed in 1927, two years after the first attack of hematuria.

After the bladder was opened, "an infiltrating tumor was found which, when first seen, appeared as a papillary growth surrounding the urethra and growing chiefly from the right side of the trigone and the adjacent bladder wall. When an attempt was made to grasp this a portion of it came away in the sponge-stick, leaving a hollow surrounded by a ridge of infiltrated bladder wall. The base of the main tumor, about 3 by 3 cm. across, hid the urethral orifice and from it a more recent papillary infiltration of the mucosa extended around the urethra

and up the bladder wall for about 2 cm. Thirty gold seeds, each containing 1 mc. of radium emanation were implanted, the main growth being steadied by a finger in the rectum to identify its thickness, which only in one place seemed to need one needle deeper than another. . . ."

Nine years later cystoscopy showed no tumor and he died of intercurrent disease 13 years after operation, aged 90.

One case more, to illustrate the way to cure bladder tumor by electronics: Miss R., with ancient hydronephrosis and recent hematuria, had been cystoscoped the week before I first saw her. In addition to the hydronephrosis she had a red blotch on the mucosa just back of the ureteral orifice. I attributed this to the previous cystoscopy. Nephrectomy was performed and before she left the hospital she bled again. This time one could see wee papillae springing up all over the red blotch. A specimen was reported cancer, two radons were implanted and she is well today, 13 years later.

COMMENT

Dr. McLellan has recently controlled two epidermoids; one of them has remained well for a year, the other for two. I permit myself to imagine that both may be cured. Note that the grade 3 tumors that lasted five years did well.

The chart (fig. 1) does not record periods of freedom from tumors of less than 5 years duration; they did not seem worth bothering about.

Of the 42 patients followed 5 years or more, 21 were papillomata or grade 1: 10 of these were controlled 5 years or more. Thirteen were grade 2: 7 of them were controlled 5 years or more. Three were grade 3: they were controlled 9, 15 and 17 years and one other recurred and died, grade 3.

Twelve were conquered within a year, all by radons. One of these was controlled 6 years, two 7, one 8, two 9, and one each for 11, 13, 14, 15, 18 and 20 years.

One cancer patient, not on the chart, was cured 31 years by a single fulguration.

79 E. 79th St., New York 21, N. Y.

DISCUSSION

Dr. Benjamin S. Barringer (New York, N. Y.): I think we should all be very grateful to Dr. Keyes for giving us the results of these 119 cases. I am particularly grateful because I am next week giving a paper at the A.M.A. showing 5-year controls and getting about 36 per cent: 5-year controls of patients that are proved cancer pathologically.

In the case that Dr. Keyes followed 7 years, I should like to tell Dr. Keyes that I followed her 22 years, and she died at the age of 92 of something or other; I don't think it was cancer; I suspect it was old age.

These are radium results. For the operative removal of the bladder cancers we have the work of Beer and Verne Hunt, who excised these tumors. They got good results. As I remember it, in selected cases they both got something like 35 per cent, 5-year controls.

Following that, there has been a period of a good deal of confusion. People have been trying to control these tumors not by fulguration of the papilloma, as was Beer's original idea, but by transurethral resection instruments for cancer of the bladder.

Then we come down to the total cystectomy period, which is at its height now, apparently.

This is certainly one of the most beautiful of all, complete and ingenious operations ever devised, and I think that we should be proud of the part that urologists have played in perfecting the operation and so lowering the mortality from the operation.

I believe at the present time we should have a certain amount of data which would be, to me, very illuminating on the total cystectomy cases, and that we ought to be able, more or less accurately, to answer the two questions which puzzle me. Of course we know that the mortality has dropped. But what cases should be operated upon by total cystectomy? Do we choose cases, or do we operate upon all cases of bladder tumors by total cystectomy? What do we do? And what are the 5-year controls of cases operated upon by total cystectomy? That would help clear the air a good deal if we could get those data, and I am sure that there are members in this audience today who can give us those data more or less accurately.

So we have three methods: the radium, excising the tumor, and total cystectomy. I threw out fulguration as no report has reached me that I have been able to evaluate.

Let me say just a word about Dr. Davis' ingenious and beautiful paper. I can't imagine that it was a carcinogenic agent which he stopped coming through the bladder which caused the recession of the tumor. That may be so. Certainly there are a great many cases reported that left the coal-tar field where they are subjected to carcinogenic agents, had left it for 10 years or more, when the tumor appeared. It would seem incredible that any coal-tar products would appear in the urine long after the patient had left a chemical works.

My impression is that of the dogs we have used, those fed betanaphthalene developed cancer of the bladder, and they take 18 months to 22 months to develop the cancer. In dogs which have been fed betanaphthalamine the drug disappears from the urine in about 3 days after stopping the drug.

Dr. Reed M. Nesbit (Ann Arbor, Mich.): I should like to ask Dr. Keyes whether in the patients enumerated on the last chart any of the radon was inserted by transurethral methods.

Dr. Keyes: A minority were treated by transurethral methods.

Dr. George F. Cahill (New York, N. Y.): Concerning the report of Dr. Davis, the occasional spontaneous disappearance of carcinoma has long been known. Occasionally it has been removed by relatively minor measures, as curretage in uterine carcinoma. We have had several similar experiences such as his, in which a tumor of the bladder was observed, biopsied and diagnosed as malignant. But after the ureters were transplanted into the intestine and the bladder removed, no tumor could be demonstrated in the bladder after careful study, and we have had the reverse of this in which the ureters were transplanted and the tumor spread so rapidly that the bladder could not be removed.

We have not seen many tumors that we could definitely say were the result of contact with aniline dyes. We notice, however, that urothelial tumors occur where urine is most constantly in contact with the urothelium. Occurring with a thousand bladder tumors were 40 renal pelvic tumors, 10 ureteral tumors and only 5 urethral tumors.

From intravenous studies the urine is shown to be most often in contact with the urothelium, first in the bladder, second in the renal pelvis, and last in the urethra. This urine contact seems to be a suggestive factor in the incidence of tumors of the urothelial epithelium.

Dr. A. J. Scholl (Los Angeles, Cal.): I am going to discuss Dr. Davis' interesting cases. There is one element that he is overlooking in the disappearance of these tumors. That is the disturbance of the blood supply. To do an ureteral transplant, he probably explored and freed up the bladder, disturbing the blood supply. I followed 1 case 15 years after opening the bladder, finding an inoperable tumor, and handling it for 15 or 20 minutes wondering whether it could be removed or not, greatly disturbing the blood supply.

Five years after we had closed his bladder, leaving the growth as being inoperable, he returned with an upper urinary tract infection. Cystoscopy revealed no evidence of tumor. He lived for 15 years and died of upper urinary tract disease.

Dr. Robin Pearse (Toronto, Ontario, Canada): The first case of recession of bladder tumor following diversion of the urinary stream which I encountered was that of a man who had a tumor $\frac{3}{4}$ inch in diameter with a short pedicle, obviously an infiltrating tumor.

Ureterosigmoid anastomosis was done, and later when the bladder was opened after the cystectomy, it appeared to be perfectly normal. However, I remembered the position of the tumor, and when the pathologist made sections of this portion of the bladder carcinoma cells were found in the muscle layer and none in the mucosa or submucosa.

Following this, Dr. McComb made it a practice to reexamine the bladder with the cystoscope before doing cystectomy, and in one of his patients the tumor entirely disappeared. However, in this case, unfortunately, the pathologist could find no trace of carcinoma in the muscle layer, so we had to admit that we might have been mistaken as no biopsy was taken previously. These 2 cases were reported during discussion at the American Urological Association meeting in New York in 1942. At the end of the session 4 surgeons came to me and said they had also had similar patients, but had not had the courage to report them.

Dr. Keyes spoke of the longevity after diathermy through the cystoscope. In 1920 I inherited a patient whom Dr. Buerger had treated in 1912 by diathermy through the cystoscope. This patient remained free of recurrence for 11 years and then had a small recurrence, which was destroyed by diathermy through the cystoscope. He then disappeared for 6 years and returned with a marked haematuria due to a pedicle carcinoma, which was removed by transurethral resection. There was one small recurrence 24 months later. He has been free from recurrence to the present date, and is reporting every 6 months.

Dr. John K. Ormond (Detroit, Mich.): I haven't kept up with the literature of the experimental work on cancer of the bladder. I would like to ask a question, which can be answered either by Dr. Barringer or Dr. Davis. Are there any records of cancer developing from use of betanaphthalene after the urine had been diverted; and, also, are there any records of cancer developing in the bowel where urine had been diverted to the bowel?

Dr. William P. Herbst, Jr. (Washington, D. C.): I should just like to discuss the most interesting cases of Dr. Davis', and recall that Dr. Georgine Luden in 1922 observed that over a hundred authentic cases of inoperable extensive carcinoma definitely regressed and disappeared. These were all authentic, proven cases.

I should like to present the idea of the psychochemical influence on our economy. We hear a lot about psychosomatic medicine. Today it seems to me that we have come to a point in our ability to recognize certain chemicals whose percentage amount in our body fluids bears a definite relationship to psychic states, as for example the concentration of the ketosteroids in patients before and after prefrontal lobotomy.

Dr. Edwin Davis (Omaha, Nebr.): I have little or nothing at all to add. These conflicting opinions and observations serve merely to emphasize what we already know, that is, that we know little or nothing about this subject. It is to be hoped that perhaps we may be on the threshold of knowing something about it—not right away, perhaps, not in our lifetime, but perhaps pretty soon.

Dr. Archie L. Dean (New York, N. Y.): I should like to discuss Dr. Davis' paper just for a moment. Our experience has been similar to his. We have noticed the disappearance of ulceration in, I would say, at least half a dozen patients, and we have seen improvement in the bladder even when complete disappearance of ulceration has not occurred with such regularity that we don't think it unusual. At the same time, it doesn't always happen, and it doesn't happen frequently in the most seriously ill patients.

There are some patients with extensive tumors of the bladder who are operated

upon for relief of their symptoms, pain, as Dr. Pearse suggested, and hemorrhage. They have been sent home with no idea of performing a cystectomy because of the advanced state of disease and poor general health, but instead of improving, their tumors have bled so seriously that a cystectomy was performed to save them from dying of hemorrhage.

I should like to describe a patient somewhat similar to Dr. Davis' who had a carcinoma of the urethra. This woman came to me 3½ years ago because she had great difficulty in voiding. That was due to obstruction of her urethra by an extensive tumor. In her left inguinal region, there was an enlarged node 6 by 5 cm. in size, which proved cancerous by aspiration biopsy. The urethra lesion was a grade 3 tumor. Her ureters were transplanted into the bowel, and nothing else has been done. She is enjoying excellent health now. There is an extensive but sclerotic cancer in the urethra, and the inguinal node has decreased to about 1 cm. in diameter. Proved cancer is still present in each area, but the palliation has been most gratifying.

Since I was brought up urologically by Dr. Barringer and Dr. Keyes, I have complete sympathy with their use of radiation, and I follow those methods. I believe that extensive surgery consisting of diversion of the urinary stream and total cystectomy is simply another type of treatment which may be valuable in carefully chosen cases.

What I practice is to make at least one strenuous effort by any of several forms of treatment, to cure a patient and still preserve his bladder. When this effort has failed, then I think the radical operation can be considered.

A small point which might be of interest is that there has been no greater difficulty in removing the bladder of patients following the implantation of radon seeds than in patients who did not have radon seeds previously.

We can answer one or two of Dr. Barringer's questions, but enough time has not passed to give authoritative answers to them all. There is an approximately 15 per cent mortality associated with radical surgery. We follow these patients quite accurately, because we hardly ever permit them to leave the hospital between diversion of the urinary stream and cystectomy. Enough time has not passed to give clear-cut end results comparable with radium results of patients treated 10 to 25 years ago. It should be pointed out, however, that it will always be difficult to compare radiation results with those following radical surgery because the two methods are not substitutes the one for the other but are employed most efficiently in different groups of patients.

DR. BENJAMIN S. BARRINGER (New York, N. Y.): May I say a word about the diversion of the urinary stream? We have not done that; it is difficult to do it. We may do it some time or other. I don't like this operation anyhow, but I did divert ureters in one dog. We washed the bladder out after that, and Dr. Dobriner found no betanaphthalene in the bladder washes. The next day the dog scrached his wound open and died.

ANASTOMOSIS OF THE VAS DEFERENS AFTER PURPOSEFUL DIVISION FOR STERILITY[1, 2]

VINCENT J. O'CONOR

From the Departments of Urology, Wesley Memorial Hospital and Northwestern University Medical School, Chicago

Vasoligation, or surgical sterilization of the male, is done for various reasons: a) With the idea of preventing the insane, the criminal or the perverse from producing offspring; b) because the wife's health is said to be too precarious to risk bearing children, the wife being unable or refusing to undergo tubal ligation;

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon N. J., June 6, 1947.

[2] *Sterilization: A short summary of its legality and history.*

Human sterilization for social good has been one of the most active and controversial legal problems of the last 40 years.

Legislation regarding sterilization of human beings was first introduced and attempted in the United States in the form of a measure introduced in the Michigan Legislature in 1897. This bill was defeated by a slight margin. The first bill to secure legislative approval was voted by the Pennsylvania Legislature but this was vetoed by the Governor in 1905. The first statute to receive both legislative and executive approval was passed in 1907 by the Indiana Legislature. Later, in 1920, this act was held unconstitutional because of its violation of the due process clause. Indiana has since passed and has had sustained the present Indiana sterilization statute.

It was not until 1927 that legislation of this type was tested in the Supreme Court of the United States. In the celebrated case of Buck v. Buck involving the Virginia sterilization statute, the Supreme Court through Mr. Justice Holmes upheld the constitutionality of a statute providing for the sterilization of the insane and feeble-minded. He announced the approval of the statute as a therapeutic measure by stating this to be "a means of coping with the socially undesirable in our midst."

Twenty-nine states have statutes providing for sterilization. Of these, 12 provide for the sterilization of criminals in addition to the insane and feeble-minded.

Various types of criminals are made subject to sterilization, although legal requisites in the main call for definite establishment of the subject as habitual criminal guilty of felonious crimes involving moral turpitude. California requires that the person have been committed to prison at least 2 times for rape, assault with intent to rape or seduction, or at least 3 times for any other crime and shall have given evidence that he is a moral or sexual degenerate or pervert. Delaware makes subject all habitual criminals who have been convicted of at least 3 felonies. Washington makes subject those convicted 3 times of felonies and who served time therefor. Four states, Idaho, Nebraska, Iowa, and Oregon, do not define habitual criminals, leaving it up to the courts. Connecticut and North Dakota provide for sterilization in the case of any inmate of any state institution likely to produce children with criminal tendencies. Kansas makes the additional provision that there be likelihood of defective or feeble-minded children with criminal tendencies. Wisconsin provides for sterilization if the Board feels that it is inadvisable that the criminal procreate; Utah also permits the same treatment of inmates with habitual degenerate sexual tendencies.

The following states do not permit sterilization of criminals but restrict its use to mental defectives, insane and feeble-minded: Alabama, Arizona, Indiana, Maine, Michigan, Minnesota, Mississippi, Montana, New Hampshire, North Carolina, South Carolina, South Dakota, Vermont, Virginia, and West Virginia. In all other states of the Union sterilization is illegal and prohibited except as incidental to medical therapy.

A majority of the states have held sterilization of criminals to be unconstitutional, as a cruel and unusual punishment within the definition of the Constitution.

Defectives are determined by Medical Boards appointed and functioning in pursuance of the various sterilization statutes.

Although sterilization has been legal in the above named states for an average period of 20 years, the states have averaged less than 50 sterilizations per year. Although science has demonstrated the inheritability of socially undesirable characteristics and traits, the God-given right of man to procreate is still a most compelling conclusion, resulting in the use of sterilization only in the most hopeless cases.

c) an agreement between husband and wife to prevent pregnancy; d) to prevent the occurrence of epididymitis, a routine procedure in many clinics in the treatment of prostatism; e) for the purpose of rejuvenation (Steinach), a false physiological assumption and a clinical failure; f) mass sterilization for the purpose of racial limitation, or extermination, as evidenced by recent Nazi treatment of persons of Jewish, Polish and other nationalities.

Because of the situation created in Europe by the mass sterilization procedures of bilateral vasoligation, or vas resection, this subject has recently been a matter of considerable discussion on the part of non-medical persons.

Members of certain branches of the clergy have taken a very active interest in this subject because of the marital implications resulting from this, ordinarily uncommon, premarital procedure. As far as we can determine, the general impression of all groups, lay, medical and religious, has been to the effect that restitution of the normal lumen of the vas is not only a very difficult surgical procedure but also successful re-anastomosis is so uncommonly attained as to make the procedure hardly worth undertaking. It is quite evident that many of these discussions have confused the procedure of epididymo-vas anastomosis with reunion of the vas itself.

The individual who seeks to have himself sterilized by vasoligation does so secretively and for, what he considers, strong personal reasons. The idea that vas ligation will be the solution of his problems is often conveyed to him by his family doctor. The latter then refers him to a surgeon, usually a urological one, for the operative procedure. The patient frequently encounters difficulty in persuading a competent surgeon to perform this procedure because in most states there is question as to its legality and the surgeon exposes himself to a possible malpractice suit. Aside from the legal aspect there are often strong psychic, moral and religious reasons which the patient may have to overcome in order to justify the operation. It is natural, therefore, that in a private practice, in normal times, one would rarely encounter an individual who sought restoration of fertility by another operation after having purposely submitted to vasectomy. For this reason no surgeon has individually had a large experience in attempting re-union of the vas after clean ligation.

A careful review of the literature reveals no observation of note on this subject. An occasional article describing a successful re-union of the vas was all that could be found. It seemed to me that a serious review of this subject would be worthwhile.

In 1919 I assisted Dr. William C. Quinby when he successfully re-united the left vas deferens in a patient who had purposely undergone bilateral vas resection in 1911. I have had the opportunity of verifying the success of this procedure by examining this man periodically for a period of over 25 years.

Since 1920, we have performed re-union of the vas in 14 patients who had previously been sterilized by bilateral vas resection. Nine of these 14 men had a successful outcome as evidenced by a careful series of follow-up examinations over a period of from 2 to 15 years. The interval between vas resection and reunion was from 5 to 18 years with an average of 8 years. In every instance the

epididymis, on one or both sides, contained many motile spermatozoa. In all of our patients bilateral re-union was done. The operation was not successful in 5 patients, one of whom was operated upon twice in a period of 3 years. The cause of failure in these patients was not apparent to us.

An attempt to pool the knowledge of urological surgeons on this subject was made by sending questionnaires to 1,240 recognized specialists. The following questions were asked:

1. How often have you attempted surgical re-union of the vas after its division for purposeful sterilization or when it had been ligated to prevent epididymitis?
2. In how many instances was the re-union successful as evidenced by the finding of spermatozoa in the semen?
3. Would you give a simple, brief description of the technique used?

Seven hundred fifty (750) urologists were kind enough to answer the above questions; many of these replies were in detail and showed a considerable interest in this subject. The following table will, in brief, summarize this information.

Questionnaires sent	1,240
Replies	750
Had never attempted the operation	615 surgeons
Operation performed 1 or more times by	135 surgeons
Results Reported	
Number of operations performed	420
Operation a failure	239
Operation a success	160
Said to be a success but result really undetermined	31

The 31 patients in whom the result is tabulated as undetermined were never examined after the operation but in each instance the wife was reported as having become pregnant.

No request was made for information on the incidence of proven spontaneous regeneration of the vasa after resection. However, 55 supposedly authentic instances were reported in the replies and in each instance it was claimed that sections of the vasa were removed and examined microscopically at the time of operation. As one prominent urologist remarked, "I have noted several instances of proven spontaneous regeneration but have never attempted an operation to restore the lumen. If nature can do it so easily, why can't we?"

TECHNIQUE

The operation for re-union of the vas should be made as simple as possible (fig. 1). I have followed the method used by Quinby which consisted by freeing the embedded ends of the vas for a distance of 1 to 2 cm., and after cutting away the occlusion scars at either end, performing an end-to-end anastomosis. In all our patients we performed incision or puncture of the epididymis (globus major) and verified the presence of active spermatozoa. In the first 6 patients we operated upon we tried to verify the patency of the vas lumen by passing a strand of silkworm-gut to the region of the ejaculatory duct. The injection of methylene blue with recovery from the posterior urethra by catheter was done in 4 patients.

Since operation was a failure in the fifth and sixth patients after this manipulation, we decided that the risk of trauma in this verification of lumen patency might defeat the purpose of the procedure. The last 8 operations were done by end-to-end anastomosis using a strand of silkworm-gut as a splint for a distance of 2.5 cm. above and below the juncture, the strand being brought out through the lower portion of the vas and through the scrotal incision. This splint was removed in from 6 to 10 days. In response to a request for a simple description

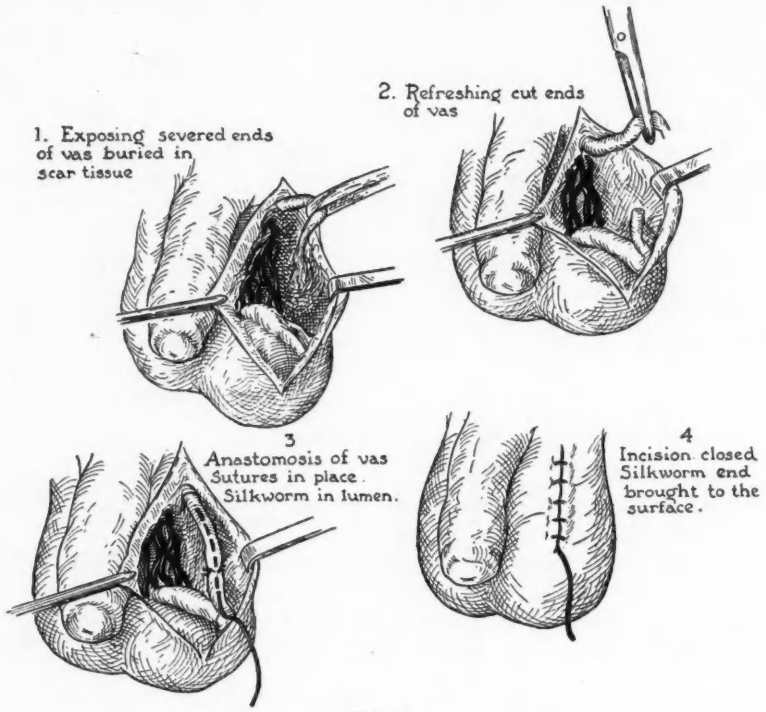

FIG. 1.

of technique, the following information was gained from the 135 surgeons who had performed the operation:

End-to-end anastomosis	305
Side-to-side (lateral) anastomosis	29
Splint used (420 operations)	299
Material:	
Silkworm-gut or Dermal	134
Horsehair	25
Tantalum wire, Stainless steel, Silver wire	140

BILATERAL URETERAL OBSTRUCTION DUE TO ENVELOPMENT AND COMPRESSION BY AN INFLAMMATORY RETROPERITONEAL PROCESS

JOHN K. ORMOND

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The following 2 cases I deem worthy of presentation to you because not only are they unique in my experience but I have so far been unable to find any similar cases in the literature.

The first case is that of a Greek male whose age was 45 when first seen by us in June 1942. His complaints were substernal pains radiating down the inner surfaces of both arms; low backache of 4 months duration, radiating down both thighs but especially the left; and loss of 10 pounds in weight in the previous 5 months.

There was nothing of special interest in his family and past histories except that his father had died of Bright's disease and his mother was hypertensive.

General physical examination showed as follows: Weight 139½ pounds. Ocular reflexes normal. Tonsils small. Teeth in good repair. No general lymph gland enlargement. Lungs and heart clear to auscultation and percussion. Blood pressure 138/100. No hernia. No abdominal masses or tenderness. No costovertebral tenderness. No abnormalities of bones and joints. Deep reflexes normally obtained. Prostate not unusual. There was a small right hydrocele.

Urine: specific gravity 1.033, no albumin, sugar, or red blood cells, but a few pus cells. Hemoglobin 10.8 gm. per 100 cc. Red blood count 4,320,000, leukocytes 5,800. Wassermann negative.

A complete gastro-intestinal examination disclosed no organic lesion.

An orthopedic consultation was obtained becaused of the backache radiating to the thighs; x-rays showed slight lipping of the tenth and eleventh dorsal vertebrae; the spinal motions were normal; the right leg was a bit shorter than the left and a lift was placed under the right heel. He was put on treatment for angina pectoris.

A few days after the completion of this series of examinations he was admitted to the hospital because of sudden, unheralded and complete anuria of 4 days duration. He was vomiting and his nonprotein nitrogen of the blood was 110 mg. per cent. The next day cystoscopy was done. The bladder was normal and the catheters passed easily up the ureters, meeting no appreciable obstruction and resulting in immediate hydronephrotic drip of clear urine from both pelves. The catheters were left in place and in the first 24 hours the right drained 2000 cc and the left 1000 cc. Pyelograms showed an almost normal right kidney pelvis, the left showing some irregularities suggestive of pyonephrosis. When the catheters were withdrawn there was again complete anuria,

[1] Read at annual meeting, American Association of Genito-Urinary Surgeous, Absecon, N. J., June 6, 1947.

and they had to be reinserted. Transfusions were attempted, but caused cardiac pain and it was deemed best not to repeat the attempt in spite of marked secondary anemia. A few days later a right nephrostomy was done. No obstruction of the upper ureter was noted and the cortex seemed only a little thinner than normal. The nonprotein nitrogen became normal. On one occasion urine appeared in the bladder but thereafter none appeared, so left nephrostomy was performed at the end of 2 weeks, and the cortex of the left kidney found to be fairly well preserved. At this time he was very anemic, the hemoglobin reading being 7.6 g. per 100 cc.

The renal function rapidly improved, but not until the ureters were dilated with bulbs 8 on right and 10 on left on two occasions was the ureteral flow reestablished.

The patient was sent home voiding normally, and with both nephrostomy wounds closed. On October 23, 1942, three months after the onset of anuria, his urine contained pus and marked secondary anemia persisted. During the next 3 years he reported for observation and treatment at irregular intervals. At first the nephrostomy wounds reopened occasionally, but they remained closed after March 1943, five months after his discharge from the hospital. His urine remained infected in spite of the use of sulfa drugs; his anemia improved at first, but after a few months relapsed. He continued treatment for angina pectoris; and almost every time he reported to the clinic his ureters were dilated with bougies with bulbs 8 or 10, which passed with ease. His course was gradually downhill, the anemia persisting, the urinary infection persisting, and the renal function diminishing.

In January 1945 he was admitted to the hospital for penicillin treatment. The urine was cloudy with pus; the nonprotein nitrogen was 82 mg. per cent; his blood pressure was 175/90. Cultures at various times during the course of his illness had showed staphylococcus, hemolytic streptococcus, and B. aerogenes; and the infection had not yielded to the sulfa drugs. During this admission he was given 100,000 units of penicillin per day for 3 days, but without effect on the urinary infection.

Six months later his hemoglobin showed 7.5 g. per 100 cc blood, so he was given transfusions, this time with no reaction and his hemoglobin rose to 10.3 The phenolsulphonphthalein output registered zero in 2 hours. In October 1945 catheters were easily run up to the kidney pelvis; the urine contained pus and the indigo carmine did not appear in 14 minutes. He was again admitted for transfusions since the hemoglobin had gone back to 7 gm.

In February 1946 he was admitted in uremia and with advanced anemia and died. Autopsy showed a fibrous retroperitoneal mass covering the promonitory of the sacrum and extending up to the kidney. The ureters, which were structurally normal and showed no strictures, ran through the lateral margins of this mass, and were enveloped and compressed by it, but not invaded. The kidneys were completely destroyed by infection and back pressure. I quote from the autopsy report:

"The retroperitoneal tissues surrounding the aorta and extending from the

kidneys to below the sacral promonitory show almost complete replacement with a dense, greyish-white fibrous connective tissue mat. This tissue is 2 cm. in thickness at its thickest point and extends out to and including the ureters.

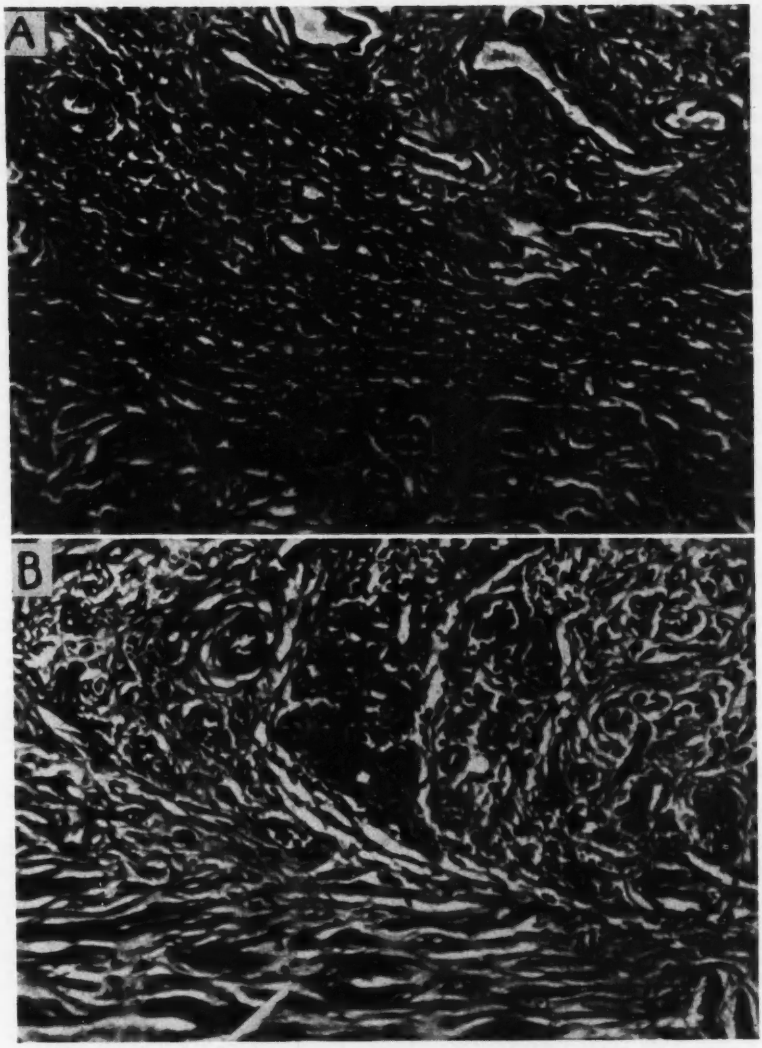

FIG. 1. Case 1. Sections from autopsy specimen of retroperitoneal tissue

The ureters, aorta and vena cava all traverse this dense mass of fibrous tissue which is sufficient to nearly occlude the lumina of the ureters.

"Sections of this dense fibrous mass (figs. 1 and 2) reveal that it is composed

entirely of extremely dense bundles of collagen. This tissue is poorly nucleated, but the cells, where seen, are of typical fibrous connective tissue type. This fibrous connective tissue surrounds without invading the large vessels, lymph nodes, nerves and ureters.

"Sections at the edge of this area of fibrosis reveal a rather sharp demarcation, but absolutely no evidence of encapsulation. The cells composing this area of fibrosis are all extremely small and show no evidence of malignancy. In one portion the fibrous tissue is invading the surrounding skeletal muscle, which shows, as previously surrounded muscle is examined, a gradual atrophy and disappearance. This fibrous tissue has no sign of malignant characteristics and has rather the appearance of a keloid."

The second case is that of a man whose age was 43 when he first came under

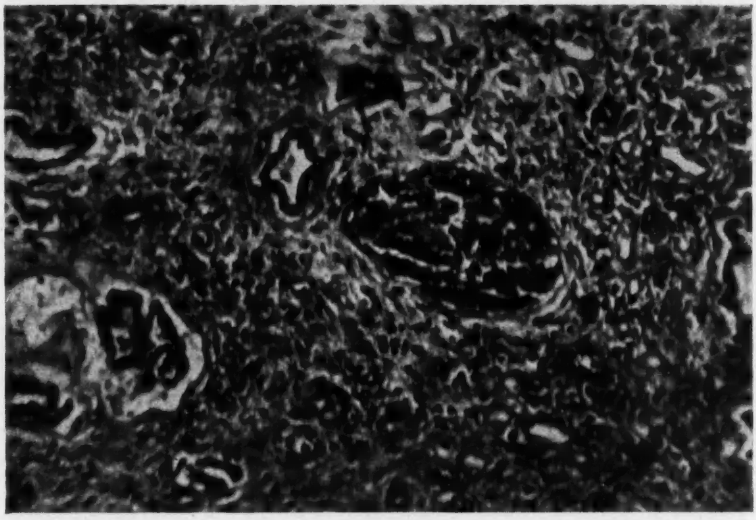

FIG. 2. Case 1. Section from autopsy specimen of retroperitoneal tissue

urological observation in January 1946. Previous to this he had been under observation by various divisions of the Henry Ford Hospital over a period of about 22 years, so his past history was well known to us. He was never robust, was always under par, and showed a mild secondary anemia over several years.

In 1924 cholecystectomy and appendectomy were performed. Following this he had a wound infection that cleared up in 3 months.

Between 1924 and 1943 he received attention at various times for upper respiratory infections, furuncles in various regions, hypothyroidism, and in 1941 an attack of bacillary dysentery. As this period is reviewed the impression is gained that he was a man rather unusually subject to infections. At no time in this period did the urine show any abnormality and the blood Wassermann test was negative.

In 1943 he first complained of lumbo-sacral backache and late in 1945 the

back pain became severe. X-rays showed calcification of the intervertebral disc between the eleventh and twelfth thoracic vertebrae and a number of calcified glands in the right lower abdominal quadrant. There was one large dental abscess.

In January 1946 the back pain increased. Neurological examination gave normal findings, so his back was strapped, but with no relief. At this time he was seen in urological consultation because of the backache associated with ache in the testicles. The urine was clear, of normal specific gravity, and routine examination of the genito-urinary tract gave no indications for more extensive examinations. In February the back pains became so severe as to require Demerol for its relief. At this time the blood showed hemoglobin 11 grams per 100 cc, red cells 3,860,000, leukocytes 8,250; urine, specific gravity 1.032, no albumin or sugar, and no red blood cells or pus cells. An x-ray of the urinary tract showed no abnormality. His pain increased, being worse at night. Barium enema and chest x-rays showed nothing abnormal.

A pantopaque myelogram showed some suggestion of a pressure defect in the region of the third lumbar disc and also in the region of the lumbo-sacral articulation. So on February 15, 1946 a bilateral laminectomy between the third, fourth, and fifth lumbar vertebrae was done. Some extradural adhesions to the lumbar nerves were freed and the presence of some varicosities noted.

It was noted on March 19 that there were no urinary or gastro-intestinal symptoms; that the back symptoms were largely relieved, but that there was pallor, asthenia and no gain in weight. The prostate was again examined but it showed nothing suspicious. On March 25 there was sudden complete urinary suppression, without any pain.

Physical examination showed no general or local lymph gland enlargement; the thyroid was not enlarged; heart and lungs were clear to auscultation and percussion; blood pressure 138/100; no abdominal tenderness or masses; no abnormality noted so far as bones or joints were concerned except the recent operation on the back; deep reflexes were normally obtained. The Wassermann test had always been negative. Catheterization showed no urine in the bladder. Cystoscopy was done and catheters passed up both ureters, finding urine in both pelves. Pyelograms were unsatisfactory, but some dilatation of the pelvis on the left was noted. The catheters were left in place and dripped continuously for some hours. Next day they became plugged and were withdrawn. The one on the right was re-introduced all the way to the pelvis, but that on the left would pass only part way, although urine dropped from it freely. With these catheters in place the nonprotein nitrogen fell in 3 days from 73 mg. per cent to 24 mg. per cent. When the catheters were withdrawn no urine reached the bladder and it was necessary to re-introduce them.

Because of his anemia and of the puzzling character of his course in the past, it was suspected that the ureters might be involved in some malignant process, and the decision was made to explore the abdomen.

On April 4, 1946 a right para-median lower abdominal incision was made. The peritoneal surfaces were smooth, the kidneys felt normal, the liver was not

enlarged and no nodules were felt on its surface. The gallbladder had been previously removed and there were numerous adhesions in this region. A retroperitoneal flat mass with indistinct lateral margins was felt covering the promonitory of the sacrum. A bit of this was removed for biopsy and frozen section showed it to be inflammatory in nature. I quote from the pathological report:

"Sections of the retroperitoneal tissue reveal alternating areas of dense, fibrous, connective tissue and fat (fig. 3). Throughout the entire sections examined is a diffuse infiltration of small, round and wandering cells, occasional eosinophils and polymorphonuclear leukocytes. In some instances the lymphatic cells are collected into small follicles. Considerable fibroblastic activity

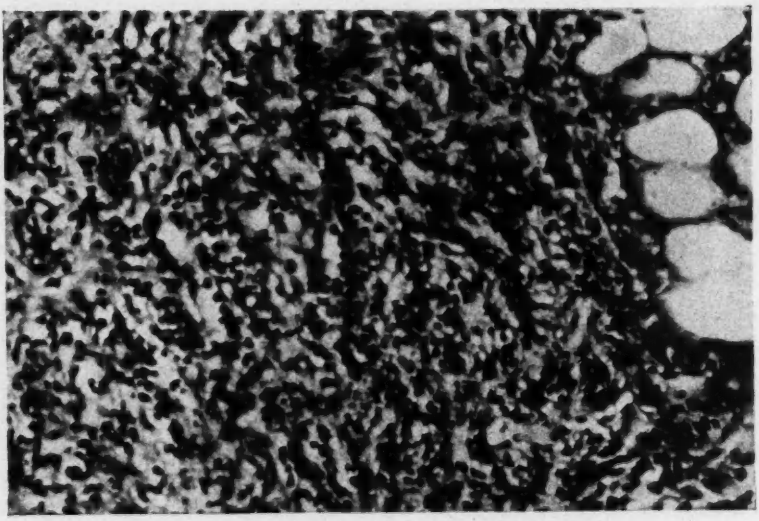

FIG. 3. Case 2. Section from biopsy of retroperitoneal tissue

is seen but no abscesses are present and there is no evidence of a specific etiology. There is no microscopic evidence of a neoplastic process."

The ureters were located below this mass, traced up, and found to pass through this tissue near its lateral margins. Both ureters were dissected entirely free from this enveloping tissue and seemed entirely normal. They were left free in the abdominal cavity, no attempt being made to cover them with peritoneum. The abdominal wound was closed with drainage because of oozing. The ureteral catheters were removed in the next 2 days. Wound healing and convalescence were uneventful and there has been free and normal urination ever since. He was given deep x-ray therapy directed at the inflammatory mass described above, and his health has improved remarkably. He is no longer anemic, has put on weight, is working regularly and feels the best he has felt in several years. We have followed his kidney condition by means of the phenolsulphonphthalein test and excretory urography. The phenolsulphon-

phthalein output has been normal and his last urogram showed no evidence of ureteral obstruction.

On May 13, 1947 a cystoscopic examination was done. The bladder seemed everywhere normal. Indigo carmine appeared from the left ureteral orifice in 3 minutes and from the right a few seconds later. A catheter was easily passed up the left ureter, but it could not be engaged in the right ureteral orifice.

On May 19, 1947 a phenolsulphonphthalein test showed 60 per cent in the first hour and urinalysis showed as follows: specific gravity 1.024, no albumin or sugar, no pus cells, occasional red blood cell.

DISCUSSION

Here are reported two instances of ureteral compression due to envelopment by a retroperitoneal, non-malignant mass. In both instances there was sudden, complete anuria. In both there was a preceding period of reduced health, unexplained anemia, and backache. In neither had there been any preceding urinary disturbance. The microscopic appearance of the retroperitoneal tissue in the 2 cases shows some similarity or relationship between them. In the second case the tissue is obviously inflammatory in origin and fairly recent or acute. In the other it could well be in the nature of scar, or the result of past inflammations. In other words, it is conceivable that the tissue from the first case represents a later stage of a process of which the tissue of the second case represents an earlier stage and this would be in accord with the different periods during which each was observed.

We were much puzzled by the course of events in the first case. We could not detect any ureteral strictures. Ureteral catheterization was always easy, yet there was pelvic retention of urine, and persistent and increasing pyelonephritis, and renal deterioration.

As I look back on it, it seems that we were rather stupid not to recognize that there was ureteral obstruction of extra-ureteral origin and that we should have explored the abdomen. It seems likely that had we done so and freed the ureters as we did in the second case, the result would have been very different.

It seems highly probable that the backache in both instances was due to the inflammatory retroperitoneal activity, and it seems possible that the reference of that ache, in one case to the thighs and in the other to the testes, was due to irritation of the ureters as they became involved in this enveloping and compressing tissue.

We have no theories to offer as to the genesis or development of these inflammatory masses or processes. It is possible that they have something to do with the lymph glands of this region, but there is in neither case any history of preceding infection of the genitalia, legs, urinary tract, or of any evidence of diverticulitis of the bowel. The possibility of brucellosis has been suggested. This could not be proved now and was not suspected at the time. I do not know whether this is a new observation or not. It is certainly new to me and to our pathological department but it is entirely beyond the bounds of possibility that there have been only two instances of this condition.

Since the process is not invasive it would probably make its presence known as it developed and spread only by the result of compression of the neighboring structures as they became enveloped by it. Of these structures the ureters would be most apt to give unmistakable evidence of their compression.

Both these patients had severe backache, which may be attributable to this inflammatory process, but obscure backaches are common and rarely demand radical or emergency treatment, while complete obstruction of the ureters urgently demands attention.

In a thorough review of the urological literature I have not found similar cases reported. If I have overlooked any reports or if any of you have seen such cases, I shall be much interested to learn of them.

OBSERVATIONS IN THE USE OF INOSITOL IN ADVANCED MALIGNANCY OF THE GENITO-URINARY TRACT[1,2]

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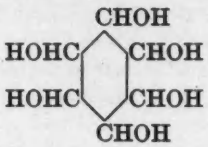
Inositol is an experimental, nutritional compound and is regarded as a member of the vitamin B complex group and has the following chemical formula:



It is found as a normal constituent in the cells of practically all plant and animal tissues. Large amounts have been found in yeast, molds and certain species of bacteria. It has also been isolated from animal tissues and body fluids such as skeletal and heart muscles, lungs, liver, brain, blood, milk, urine, eggs, etc.

A number of different forms of inositol are known. It exists in the liver in an alkali-labile combination with a large molecule, presumably a protein. A combined form exists in heart muscle and possibly other types of muscles. Some inositol occurs in the free state. In plants the majority is present as phytin, which is the calcium and magnesium salt of inositol. In the tubercle bacillus and the soybean, inositol is in combination with the phosphatide fraction as a glycoside.

It is an extremely stable compound with a slightly sweet taste, soluble in water but insoluble in absolute alcohol or ether. It can be determined in tissues and foods by means of a microbiologic assay employing a specific strain of yeast as the test organism, or by chemical methods.

Inositol was first recognized as an important factor in animal nutrition by D. W. Wooley in 1940, who isolated the substance from liver and found that it cured a disease in mice which was of dietary origin and was characterized by retarded growth and alopecia. It has also been shown to be a growth factor in the chick, in young mice and in rats. Its addition to a highly purified diet practically doubled the growth of cotton rats.

In June 1943, it was reported by Laszlo and Leuchenberger that intravenous injections of inositol were found to inhibit tumor growth in mice, the degree of inhibition depending upon the dose injected. It also acts as a lipotropic factor, preventing the development of fatty livers.

Observations by Martin, Thompson and co-workers have noticed a marked increase in the peristalsis of the stomach and small intestines in animals receiving

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 6, 1947.

[2] Inositol was furnished by the Department of Research Medicine of the Winthrop Chemical Company.

inositol suggesting it might be a nutritional factor affecting gastro-intestinal motility.

It is suggested by Abels, Ariel and co-workers that patients with fatty infiltration of their livers and those with gastro-intestinal cancer and bile duct obstruction who may be operated upon, should be given glucose and lipocaic (or inositol) preoperatively in order to restore toward normal their altered hepatic chemical constitution, thus increasing the resistance of their livers to damage by hepatoxins.

Several reports have appeared on the clinical use of "soya lecithin" which contains lecithin, cephalin, inositol, oils and other materials. This was found to inhibit hypercholesterolemia in animal experiments and also to a limited extent in some diseases of man. This was ascribed to the inositol content of the above preparation.

It was felt that the promising, although limited results with the use of inositol in animals and in man, that it deserved more extensive investigation before any definite conclusions regarding its therapeutic usefulness can be determined. On this basis it was used experimentally in a number of advanced cases of malignancy of the genito-urinary tract and was administered orally in dosages of 2–4 gm. daily.

The first 7 cases were terminal malignancies, composed of 4 cases of carcinoma of the prostate with extensive metastatic lesions to the bones; 2 cases of carcinoma of the penis with inguinal metastasis; and 1 case of seminoma of the right testicle with metastasis to the abdominal aortic nodes and a large retroperitoneal mass in the left abdomen with displacement of the stomach and descending colon, producing early signs of intestinal obstruction. Inositol in these cases produced practically no change in their clinical progress. They continued a downhill course and died in a short period of time.

Case 8. A white male aged 74 had a diagnosis of carcinoma of the bladder and hematuria. Cystoscopic examination revealed an extensive, infiltrating, transitional cell carcinoma extending over the left lateral wall of the bladder and left trigone. Inositol was started March 13, using 4 gm. daily. He had no bladder symptoms and no hematuria and appeared to be more comfortable. However, extensive metastasis to both lungs developed with hemoptysis. Cystoscopic examination on May 7 showed only a small necrotic growth on the left lateral wall of the bladder, about ¼ of the size of the original lesion. The patient died June 1, from pulmonary hemorrhage and we were unable to obtain an autopsy. We believe inositol had some effect on reducing and retarding the lesion in this patient's bladder.

Case 9. A white female aged 88 had a diagnosis of papillary carcinoma of the bladder with a history of intermittent episodes of hematuria of 3 years' duration. Cystoscopic examination revealed a papillary tumor over the left trigonal area of the bladder. Inositol was started June 9, using 3 gm. daily. There was no hematuria during the next 6 weeks while the patient was on this drug. Cystoscopic examination on the day of discharge, July 20, revealed a small, round, smooth elevation just above the left ureteral orifice. The patient was given

inositol, to be continued for 2 months. Cystoscopic examination 10 months later revealed no evidence of carcinoma anywhere in the bladder. She has been completely asymptomatic since discharge. We believe inositol had some beneficial effect on the retardation or even elimination of the carcinoma of the bladder.

Case 10. A white male aged 80 had a diagnosis of transitional cell carcinoma of the bladder. Cystoscopic examination revealed 3 large papillary tumors in the fundus of the bladder. Symptoms were intermittent, painless hematuria of 2 years' duration. The bleeding area was fulgurated. Inositol was started February 2, using 4 gm. daily. Cystoscopic examination June 2 revealed what appeared to be a superficial necrotic area in the region of the original tumors. Biopsy showed transitional cell carcinoma of the bladder. The patient had had no hematuria since inositol was started. He died rather suddenly in July from a coronary thrombosis. We believe that inositol had some retarding effect on this tumor of the bladder.

Case 11. A white male aged 74 had a diagnosis of carcinoma of the bladder. Cystoscopic examination revealed a large infiltrating papillary growth on the right anterior wall of the bladder. Biopsy showed transitional cell carcinoma. Inositol was started June 6, using 3 gm. daily. Cystoscopic examination July 10 revealed only a slightly raised area in the region of the original tumor. A biopsy showed transitional cell carcinoma. The patient was discharged July 22, with instructions to continue inositol. He was readmitted 9 months later with a return of the tumor which was quite extensive on examination. I do not believe this patient took any of the medication he was instructed to take on discharge, neither did he return to the outpatient clinic for follow-up studies. During his last admission he has been receiving inositol 4 gm. daily. There is still a marked increase in the size of his bladder tumor, but no hematuria in spite of a severe complicating alkaline cystitis. We believe inositol had some beneficial effect on the tumor during his first admission.

Case 12. A white female aged 63 had a diagnosis of extensive carcinoma of the bladder. Cystoscopic examination revealed a large infiltrating tumor of the right fundus and right lateral wall of the bladder. The bleeding area was fulgurated in order to control hemorrhage. Inositol was started January 4, using 3 gm. daily. The patient has had no furthur bleeding and is fairly comfortable. Cystoscopic examination, February 12, revealed a marked reduction of the size of the tumor growth. She was discharged, inositol to be continued. The patient is being followed in the outpatient clinic and has been symptom free for the past 4 months. We believe inositol had some beneficial effect upon this bladder tumor.

Case 13. A white male aged 56 had a diagnosis of hypernephroma of the left kidney. Nephrectomy was performed in September 1945. A year later swelling developed in the left side of the abdomen, and pain in the left leg. There was no response to x-ray therapy or stilbestrol. March 1947, inositol was started using 4 gm. daily. The patient has had marked reduction in the severity of the pain and has been much more comfortable since starting the drug. The mass is approximately the same size but his general response is excellent. At

the present time he requires only an occasional dose of Demerol at bedtime. We believe inositol has had a rather favorable influence on the symptoms.

As of January 1948, 2 patients have had a succession of new papillary tumors, despite inositol on a prophylactic basis.

SUMMARY

Inositol was used in 13 patients with advanced malignancy. The cases of carcinoma of the prostate, carcinoma of the penis and seminoma of the testicle, all with metastasis, as far as we could determine from their clinical course, did not receive any beneficial results from the use of inositol. However the cases of carcinoma of the bladder were definitely influenced as manifested by the disappearance of hematuria and a reduction in size of the original tumor growth. There was 1 case of hypernephroma of the kidney which has had a symptomatic response to this drug. A number of these patients are still receiving the medication and will be brought back for periodic check-ups.

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MASSIVE SPONTANEOUS HEMORRHAGE INTO AND AROUND PARENCHYMAL LESIONS OF THE KIDNEY[1]

LEON HERMAN

Evidence of recent or remote hemorrhages of small degree is commonly found at operation in and around various lesions of the kidney. But massive spontaneous bleeding is a rather rare event which may inaugurate, add to, or abruptly change the clinical picture. In the cases to be reported herewith, the initial symptoms were directly attributable to the bleeding, which in one instance caused severe pain and the sudden development of a large mass in the loin as the result of massive spontaneous hemorrhage into and around a large renal lipoma, while in the other, anuria occurred as the result of displacement and compression of the ureter, incident to intracystic hemorrhage in a case of congenital single kidney with multiple cysts.

Fatty tissue, while not a normal component of the renal parenchyma, may occur here as a true neoplasm, or in the form of replacement lipomatosis. These lesions differ widely in pathogenesis, but resemble each other somewhat in both gross and microscopic features. Lipoma is a rare lesion, usually occurring in an otherwise normal kidney, while the fat in replacement lipomatosis takes the place of diseased tissue. In a series of 46 clinical cases of the latter, collected by Kutzmann in 1936, the fat was large in amount and served to replace chronically infected parenchyma, associated in 79 per cent of the cases, by renal stones. The only exception to this rule was reported by Young who found extensive lipomatosis in a kidney free from both infection and stones. No reasonable explanation has been offered for the occurrence of this condition, but whatever its pathogenesis, the diseased parenchyma is replaced by hilar fat until merely a thin peripheral layer of uninvolved kidney tissue remains. The most extensive example encountered by us is shown in figure 1.

In 1938, Roth and Davidson stated that replacement lipomatosis is not as rare as one might expect from the number of reported cases, an opinion based on the demonstration of deposits of fat in 37 kidney specimens in the pathological museum of Ohio State University. But in many of these cases the deposits of fat were insignificant and occurred in association with various types of chronic nephritis.

The occurrence of intrarenal lipoma may be ascribed to embryonic cell rests arising perhaps as suggested by Roth and Davidson from mesodermic tissue, carried into the renal blastema by tubular elements derived from the ureteral buds. These are true neoplasms, and occur in the majority of cases as small round nodules of fatty tissue situated beneath and attached to the renal capsule. These small tumor have no clinical significance and the kidney tissue adjacent to them suffers only from compression. Intrarenal lipoma of clinical significance, of which approximately 16 are on record, are usually large and often so

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 6, 1947.

situated as to render determination of their point of origin difficult, or impossible. To the 12 cases reported up to 1941, Robertson and Hand added 2 cases, and since then, Latienda has described a case and added 1 reported by Bengolea in 1922, and apparently overlooked by Robertson and Hand. In some of the reported cases, the condition resembles replacement lipomatosis. With few exceptions intrarenal lipomata give rise to renal pain and in about one half of the cases a palpable mass is to be found in the loin. Hematuria occurs in about

FIG. 1. Extensive replacement lipomatosis incident to chronic pyelonephritis with renal calculus. Note thin remnants of parenchyma surrounding fat, which has compressed calyces.

20 per cent of the cases. In the case to be reported herewith, and in 3 of the collected series, severe renal pain could be ascribed to concealed hemorrhage In one of Robertson and Hand's cases there was extensive hemorrhage about the renal capsule and clotted blood was found between the tumor and the kidney substance. Hinz found perirenal hemorrhage of moderate degree, while in a case clinically similar to our own, Nicholson and Gillespie encountered a large mass which had formed as a result of massive hemorrhage in the region of the kidney, a large hematoma in the upper pole of the kidney and extensive subcapsular and intrapelvic hemorrhage. The lipoma in this case, which occupied the upper pole of the kidney, was small, measuring only 2.6 by 3.5 by 2.5 cm.

In an asymptomatic case reported by Robertson and Hand, certain parts of the tumor resembled hemangioma of the cavernous type, and many writers remark the richness of the tumoral blood supply. Intrarenal lipomata are usually single and large. Tumors weighing more than 2000 gm. have been reported by Grawitz and Bartsch. In 3 instances multiple tumors were found, while in a case reported by Warthin, the lipoma invaded and filled the dilated renal pelvis and extended down the ureter for a distance of 6 inches, resembling in this particular a case of mixed tumor of the adult kidney, previously described by the writer. The preoperative diagnosis of intrarenal lipoma has not been made. In 2 instances in which the tumors occupied the periphery of the kidney, urographic studies were negative, but in all other cases in which visualization was attempted, there were pelvic deformities more or less characteristic of neoplasm or cyst.

CASE REPORTS

Case 1. Large intrarenal lipoma with massive spontaneous intra- and peritumoral hemorrhage. A. W., a white male aged 54, was admitted to the Pennsylvania Hospital February 3, 1947, complaining of severe pain in the left renal area. This patient, a rugged individual of Norwegian extraction, having retired the night before in his usual state of good health, was awakened by severe pain in the left loin referred to the groin. There was no hematuria. The family physician administered morphine and sent the patient to the hospital with the diagnosis of renal stone.

The patient was pale and complained of weakness and had the appearance of one who had recently lost considerable blood. This was supported by the fact that the blood studies showed only 9 gm. of hemoglobin, 3,300,000 red blood cells and 8,000 white blood cells. The urine and kidney function were normal. A large tender mass filled the loin space and extended to the midabdominal line and midway between the umbilicus and inguinal canal. The overlying muscles were rigid. The umbilicus and surrounding tissues for a distance of one half inch or more were infiltrated with dark blood, a sign of perirenal hemorrhage not observed before by us. The genital tract was normal. The physical and x-ray examinations of the chest showed no abnormalities. Intravenous urograms were interpreted as follows: "Preliminary films show no evidence of urinary calculi. The left side of the abdomen is largely filled with a soft tissue mass, obscuring the kidney shadow. The right kidney is fairly well visualized. In the intravenous study, there is fair visualization of both pelves without gross deformity on the right. There is a gross filling defect with obliteration of the lower calyces and deformity of the lower margin of the left renal pelvis. The appearance suggests a neoplasm or cyst of the lower pole of the left kidney. The ureter is considerably displaced toward the midline at the level of the second and fourth lumbar vertebrae."

On April 5, 1947 the leukocyte count had increased to 12,500 and there was a slight rise in temperature. The tentative diagnosis was concealed hemorrhage occurring in association with a neoplasm or cyst of the left kidney, the presence

of pelvic deformity favoring this diagnosis rather than that of spontaneous or so called essential perirenal hemorrhage.

Operation (February 6, 1947): Spinal anesthesia was used. A transfusion of whole blood was given during the operation. Incision disclosed widespread hemorrhagic infiltration of the tissues and a large black mass filling the loin and extending far downward and inward. There had obviously been a massive perirenal hemorrhage and some of the blood had extravasated through Gerota's fascia and into the surrounding tissues. After incising the fascia, a large mass of clots was evacuated from the region of the upper pole of the kidney, the latter was freed and clamps placed on the pedicle and the latter cut. With the removal of more clots, possibly a quart or more in all, a blood infiltrated yellow neoplasm was exposed, apparently springing from the lower pole of the left kidney. The tumor, together with the kidney was removed in the belief that we were dealing with a hypernephroma which had ruptured spontaneously due to intratumoral bleeding. Recovery was without incident and the patient was discharged February 17, 1947.

Pathological report (Dr. Crane): "The specimen consists of a kidney, previously opened and partially stripped of its capsule, and attached fatty tissue weighing 340 gm. and measuring about 15 by 15 by 5 cm. (fig. 2). The kidney shows a smooth, brown surface on which are several unilocular, clear cysts up to 0.7 cm. in diameter. The cut surface shows a red-brown cortex 0.5 cm. wide and normally prominent and striated pyramids. However, at the lower pole the kidney tissue is flattened and blends with an irregular fatty, yellow mass that has been previously cut and fragmented. The capsule of the kidney appears to extend over this fatty tissue and the renal parenchyma is narrowed and distorted with fragments of yellow fat attached to a concave margin of renal tissue. This fatty mass extends around the renal pelvis and does not appear to be encapsulated save for the region of the renal capsule. Cut surface of this tissue is whitish-yellow and slightly firmer than normal fatty tissue. Over the fat there is an irregular coating of red-purple blood clot. In the fatty tissue in the region of the flattened cortex are 3 round, red nodules 0.2 cm. in diameter resembling thrombosed vessels. The calyces and renal pelvis are slightly dilated, but not otherwise abnormal. There is no communication of these structures with the fatty mass. The major branches of the renal artery and vein are normal.

"Sections of the main portion of the kidney show normal nephrons and blood vessels. At the flattened, lower pole the capsule and compressed nephrons and partially sclerosed glomeruli are flattened over a tissue composed of large clear, adult fat cells (fig. 3, *A*). At other points the fat cells extend out to a fibrous capsule, but near here fragments of tubules may be seen in the fat (figs. 3, *B* and 4). Closer to the preserved kidney the fat extends directly along the renal border. There is no structural wall which would suggest a cyst at any portion. Throughout the fat there are large strands composed of fibroblasts and collagen, but no mitsoses or tumor giant cells are noted. There are scattered dilated, smaller arteries containing thrombi of fibrin and necrotic red and white cells.

"This lesion, as I reconstruct it, is an intrarenal lipoma growing possibly from

the peripelvic fat originally, but finally impinging upon and compressing and distorting the renal parenchyma of the lower pole. There are no structures present resembling a clear, cell carcinoma (hypernephroma) or other tumor of the renal components proper. Diagnosis: Lipoma of kidney."

Renal cysts containing blood are commonly found at operation but the clinica

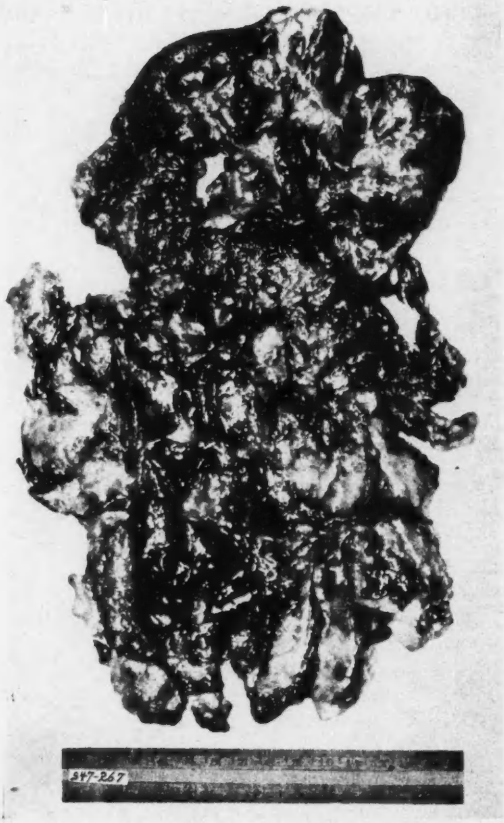

FIG. 2. Section surface of kidney with intrarenal lipoma. Upper two-thirds of kidney are intact, lower third destroyed by blood infiltrated neoplasm.

picture is rarely inaugurated as the direct result of the bleeding as occurred in the following case.

Case 2. Anuria due to ureteral compression incident to intracystic hemorrhage in a case of congenital single kidney with multiple cysts. Mrs. A. B. H., a white woman aged 64, entered the Bryn Mawr Hospital April 16, 1940 with right costovertebral pain and gross hematuria of 8 days duration. The patient, an obese, hypertensive individual, gave the history of having accidentally swallowed a

radium capsule in 1929 which was being used in the treatment of a nasal lesion. The capsule was removed 30 hours later from the distal end of the ileum. The episode was followed by serious illness with hematuria, jaundice, and delirium as prominent symptoms. She recovered after a prolonged convalescence and was in fair health until the present attack.

Physical examination yielded nothing of great importance. There was mild anemia. The urine contained blood but no pus and the cultures were sterile.

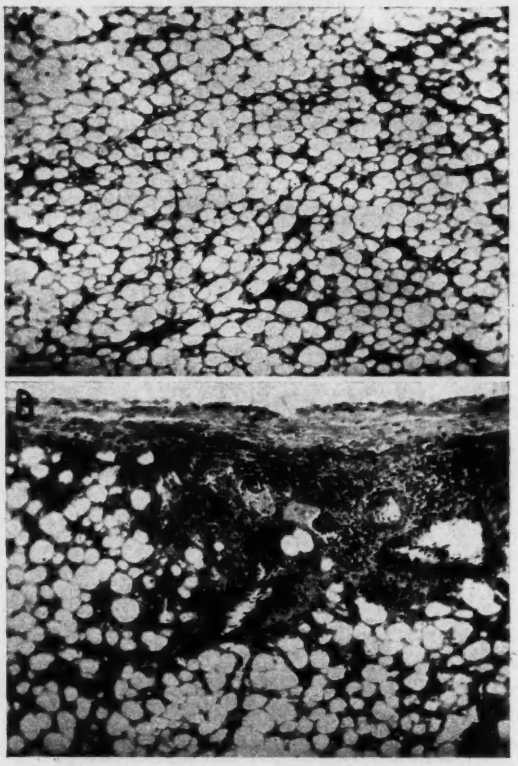

FIG. 3. *A*, Section of tumor, showing it to be composed of large adult fat cells. *B*, Section through capsule of tumor. Glomerular and tubular elements are shown between capsule and fat.

Kidney function was slightly decreased. Cystoscopic examination on the day of admission showed grossly clear urine. The left half of the trigone was undeveloped, and there were small ecchymoses surrounding the right ureteral orifice. The ureter was unobstructed, and catheterization yielded clear, followed by blood tinged urine. Phenolsulphonphthalein was eliminated from the right kidney in 3 minutes, with a total output of 60 per cent in 2 hours. No dye was recovered from the bladder. It was assumed that the bleeding came from the

right (congenital single) kidney. X-ray examination showed no shadows suggestive of stones. The outline of the right kidney seemed to be much enlarged. The left kidney could not be visualized. Secretory urograms showed faint concentration of the dye after 15 minutes. The right renal pelvis was normal in shape and size. The calyces were indistinctly shown. There was no evidence of a functioning kidney on the left side. A retrograde pyelogram was not done and the patient was discharged, with the condition undiagnosed.

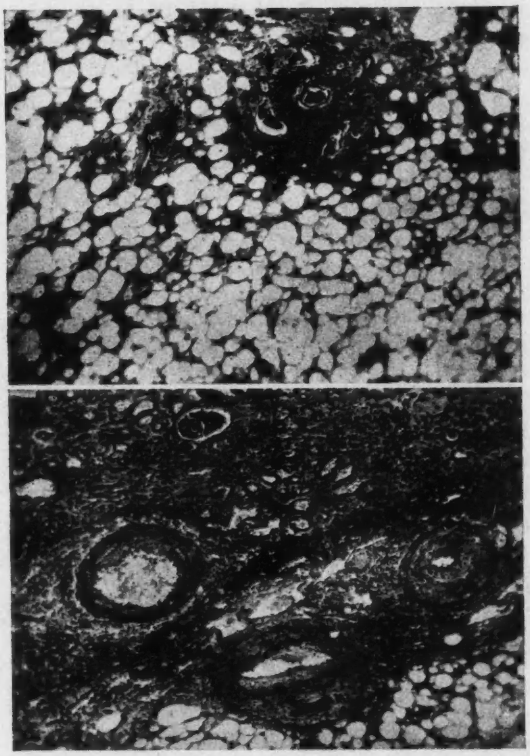

FIG. 4. *A*, Area of tumor, showing small group of atrophic tubules. *B*, Section of tumor at junction with kidney cortex, which is flattened. There is increase in fibrous tissue and tubules are atrophied.

The patient was re-admitted December 18, 1941. She had had no further symptoms referable to the urinary tract until 2 weeks previously when she noticed dimness of vision and inability to concentrate her thoughts. Suddenly at 11 p.m., approximately 36 hours before admission, she experienced an attack of severe pain in the right costovertebral angle. By the next morning she was semi-stuporous, anuric and obviously very ill. The family physician who shared our belief that there was a neoplasm involving the single kidney reported the circumstances to us, and the patient who was now comatose was immediately

brought to the hospital and taken to the cystoscopic room. A No. 5 catheter met no obstruction in the right ureter and more than 60 cc concentrated blood tinged purulent urine was aspirated from the pelvis. The catheter was left indwelling and during the following 36 hours, drained 500 cc urine, when it was accidentally removed. The catheter was replaced 6 hours later. No urine was secreted in the interval. Again there was pelvic retention without demonstrable ureteral obstruction. Large quantities of glucose solution and plasma were given and in the following 12 days the catheter drained well with a daily output averaging about 1500 cc. Strangely enough the highest urea nitrogen blood content was 49 mg. per cent. There was moderate anemia and marked hypertension.

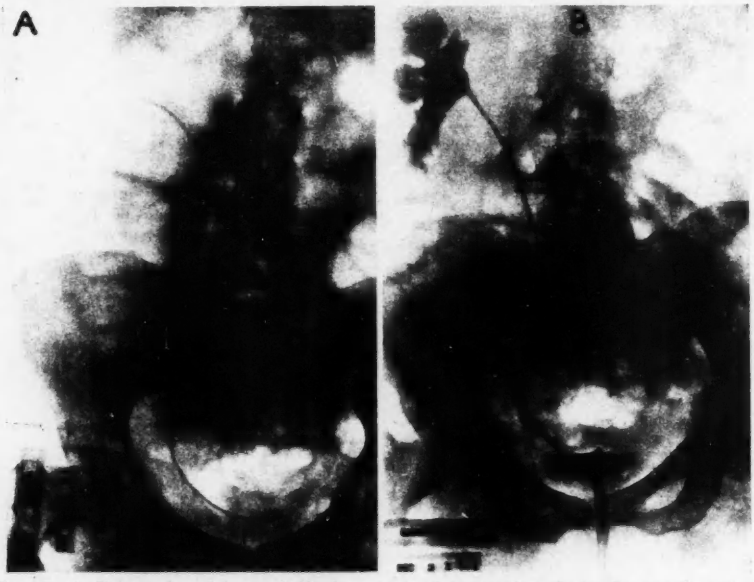

FIG. 5. *A*, Forward and inward displacement of ureteral catheter by renal cyst. *B*, Hydronephrosis with anuria due to ureteral occlusion by large renal cyst.

The eye ground examination disclosed advanced toxic amblyopia; it was not until several weeks after operation that normal vision returned. Improvement was unusually rapid and 3 days after admission the kidney secreted a total of 17.5 per cent phenolsulphonphthalein in a 15 minute period. Plain x-ray studies showed no evidence of urinary calculi. Stereoscopic views with the catheter in position showed marked forward and moderate inward displacement of the latter which after passing far forward, dipped backward to enter the kidney pelvis (fig. 5, *A*). This was confirmed by retrograde pyelograms which also showed that the kidney was displaced downward and outward and rotated so that the ureteropelvic junction was directed forward and inward (fig. 5, *B*). The pelvis and calyces were uniformly dilated but without other deformity. However, it seemed obvious that we were dealing with a retroperitoneal mass which had

arisen either from the kidney or from tissues adjacent to this organ and it seemed reasonable to attribute the anuria to pressure on the ureter from without. We did not suspect the occurrence of intracystic hemorrhage.

Operation (December 29, 1941): The lower half of the kidney was exposed through a loin incision. On the exposed portion of the rotated kidney a cyst, 3 cm. in diameter, and 3 smaller ones in size were found and incised. A very large black mass with the ureter crossing it, covered the lower pole of the kidney and extended far forward. This was found to be a blood filled cyst originating from the mesial side of the lower pole of the kidney. The cyst was incised and several ounces of heavy clots evacuated, whereupon the ureter filled promptly and the pelvis emptied itself. A large cigarette drain was placed in the cyst and the wound closed. We removed only a small portion of the clots fearing activation of the bleeding, nor did we consider excision of the cyst justifiable under the existing circumstances.

Recovery was slow but fairly uneventful. The pateint was discharged from the hospital January 26, 1942, and has had no further trouble referable to the urinary tract. The case is in our experience unique and I have failed to find a similar one among the cases reported under the title "Acute Hemorrhagic Cysts of the Kidney," by Munger and others.

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ANURIA: ITS TREATMENT BY PERITONEAL DIALYSIS[1]

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Anuria is always a medical challenge which too often terminates in fatal uremia. Its underlying cause is legion. Renal failure may be reversible or irreversible, but when anuria ensues the therapeutic difficulty lies in predetermination of this factor. It has been pointed out by others[2, 3, 4, 5, 12, 13, 14] that acute renal failure with reversible changes is frequently fatal because of accumulation of substances normally excreted, and that artificial removal of these products should lower the mortality. Fine et. al.[3, 4, 5] have defined the reversible changes as due to transfusion reaction, sulfonamide toxicity, massive trauma, toxemia of pregnancy, mercury poisoning, and acute glomerulonephritis; and state that uremia is fatal becaues the renal lesion requires more time for repair than the lethal effects of uremia will permit. This could be avoided if, during the repair period, some extrarenal excretory route could be substituted. Abbott and Shea[6] have ascribed uremic death to accumulation of toxic products, changes in osmotic pressure of the body fluid, dehydration or overhydration, and acid base imbalance. These toxic substances are not yet identified, although Gamo[7] believed they contained oxyproteic acid, and Cristol thought polypeptids. They are dialyzable and contain nitrogen.[7]

Various extrarenal excretory substitutes have been explored. In 1914 Abel, Rowntree and Turner[2] used celloidin tubes for dialysis. Putnam[8] in 1923 tried the peritoneum as a dialyzing membrane. Rhoades[9] in 1938 used peritoneal injection of fluids, and Ochsner[5] has recommended gastric lavage, 20 litres daily. Kolf and Berg[10] in 1944 used a revolving drum around which was wound a 40-

[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 6, 1947.

Invaluable assistance was given by Drs. Banks and Hoyt (pathology), Dr. J. A. MacDonald (medicine), Drs. Gatch and Owen (surgery), Drs. Smith and Sutton (residents), and Mr. Spurling Clark (pharmacist) and Nelma McClay (chemist). The expense of laboratory work was borne by the administration. Self-effacing, careful nursing was a comfort to the patient and a credit to the profession.

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yard 23 mm. cellophane tube connected to the arterial supply at one end and the venous outlet at the other. The drum rotated in a tank of solution containing NaCl 0.06 per cent, KCl 0.04 per cent, $NaHCO_3$ 0.2 per cent and 1.5 per cent glucose for 10 to 14 hours. The patient was heparinized with 1200 mg. of heparin. Eleven patients have been thus relieved out of 27 trials. Bliss[11] in 1932 found that nephrectomized dogs, which usually die in 3 days, could be kept alive for 16 days by intermittent injection of balanced salts solution into the peritoneum for ten minutes and then drawn off. To Wear, Sisk and Trinkle[7] goes the credit for the first use of peritoneal dialysis on a human being with survival. They used buffered Locke-Ringer's solution. They pointed out the importance of not removing salt, calcium and glucose in the course of dialysis. Their paper gives an excellent bibliography of the development of peritoneal dialysis. Abbott and Shea[6] commented in March 1946 that previous methods of peritoneal lavage failed because water and electrolyte balance were not considered and gave the criteria of proper solution as permitting a maximum diffusion of waste into it, the property of not altering the electrolyte pattern of extracellular fluid, having the desired tonicity and affording nutrition, and keeping protein catabolism at a minimum. Gatch (in a personal communication) has called attention to the fact that the peritoneum retains the power to filter nitrogenous wastes from the blood which is possessed by the primitive creatures from which man has evolved, the earliest form of glomerules having been a capsule of peritoneum.

Abbott and Shea[6] writing in 1946 state that peritoneal lavage has been used on 13 patients, Wear's[7] case alone surviving. Rhoads[9] classified these cases in 1938:

Ganter (1923), 1 case, chronic nephritis, died.
Heuser and Werder (1927), 3 cases, cause unstated, unsuccessful.
Balaza and Rosenak (1934), 2 cases, bichloride poisoning, died.
Wear and Sisk (1938), 5 cases, carcinoma of bladder (2), died; bilateral hydronephrosis (2), died; reflex anuria with obstruction (1), lived.
Rhoads, 2 cases, chronic nephritis, died.

To which may be added the following more recent reports:

Fine et al. (1946), 4 cases, sulfonamid anuria (1), recovered; transfusion reaction (2), died; carcinoma of cervix (1), died.
McGraw (1946), 1 case, nephritis and nephrosis nonprotein nitrogen lowered.
Flocks (personal communication) (1946), 2 cases, nephritis, died.
Creevy (personal communication) (1946), 3 cases, transfusion reaction (1), recovered; hemolysis following resection (1), died; sulfonamid anuria (1), recovered.

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Smith and Eaves (1946), 2 cases, sulfonamide anuria (1), died; hemolysis following resection (1) recovered.
Schaaf (personal communication) (1947), 1 case, sulfonamide anuria (1), recovered.
Muirhead et al. (1947), 1 case, transfusion reaction (1), recovered.
Goodyear et al. (1947), 1 case, transfusion reaction (1), recovered.
Authors (1947), 1 case, nephrosclerosis and sulfonamid anuria (1), died.

This brings the total number to 29 with 9 survivals some of which subsequently showed clinical pathologic evidences of relative renal insufficiency. Undoubtedly the method has been used more often without publication of any report. Kolf recently mentioned the use of lavage at the meeting of the Chicago Urological Society, and O'Conor has also made use of the method.

In 1946 Fine et al.[3, 4, 5] found that peritoneal irrigation would remove crystalloids from the blood with efficiency adequate to substitute for renal function and sustain life many days. They used mammalian Tyrode's solution (20 to 30 litres daily), designed to avoid plasma depletion of electrolytes, glucose to avoid acidosis, and penicillin and sodium sulfadiazine to prevent infection, and heparin to inhibit fibrin deposition. They[5] emphasize that the peritoneum is a good dialyzer, permeable to water and crystalloids, and removes the diffusable substances from the plasma and extracellular fluids. Proper adjustment of the irrigating solution prevents subnormal depletion of plasma concentration and protects the chemical structure of extracellular fluids. Experimentally they determined that peritoneal irrigation would provide 40 per cent to 75 per cent of normal kidney function (terms of urea clearance). Tyrode's solution per litre contains the following (anhydrous): NaCl 8 gm., KCl 0.2 gm., $CaCl_2$ 0.1 gm., Mg Cl_2 0.1 gm., NaH_2PO_4 0.05 gm., $NaHCO_3$ 1. gm., and dextrose 1.5 gm. All the foregoing except $NaHCO_3$ is autoclaved and the latter sterilized separately and added. In addition, the solution contains the sodium salt of heparin (0.25 to .50 mg.). The latter may be omitted if the patient is sensitive. They recommend running the solution through a Mandler filter and water bath at 40° to 45°, and thence to the peritoneal inlet at 40 to 60 cc per minute. They report 4 cases of uremia so treated with one recovery. In discussion of their paper McGraw[5] reported an instance where peritoneal lavage reduced the nonprotein nitrogen from 150 to 95. More recently Goodyear and Beard[2] reported the successful use of peritoneal irrigation for anuria caused by a post nephrectomy transfusion reaction with recovery.

CASE REPORT

The following case report is based entirely upon the method of Fine[5] with the exception that we were unable to use a filter and substituted hot water bottle jackets for the water bath. We were unable to maintain as fast a flow as he suggests because of difficulty (mentioned by others) at times with the outflow. See figure 1.

Mr. A. G. V. (No. 19407) aged 59, a white married man, entered the Methodist Hospital on November 27, 1946, saying that he "did not know why he was there." He had been pretty well until November 20, 1946, when he became

nauseated, vomited, had abdominal pain and diarrhea, black stool, and a temperature of 102. He had been taking for a period of 8 weeks 300,000 units of vitamin D a day. A specimen of urine examined during the summer was reported to have been normal. On November 23, 1946, the patient was seen by Dr. John Kingsbury who found no abnormalities in the head or chest. The abdomen was sensitive to palpation throughout. The patient was dehydrated and was thought to have a severe gastro-enteritis which was epidemic at the time. He was given twelve 0.5 gm. sulfadiazine tablets and was directed to take one 4 times a day. Sodium bicarbonate 2 gm. was given with each dose, and fluids forced. The patient took 9 tablets of sulfadiazine in all, whereupon his urine showed, on November 25, 1946, a large amount of albumin, pus cells and

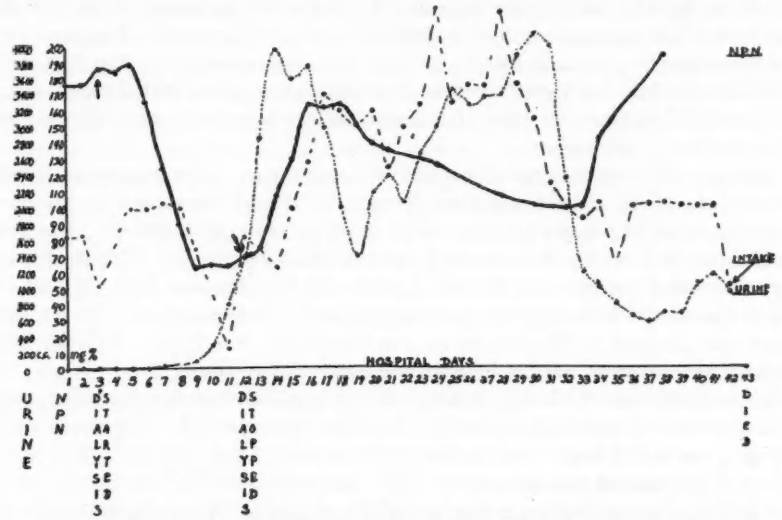

FIG. 1. Chart showing daily relation of N.P.N., fluid intake, and urinary output

red blood cells. Two days later the patient reported to Dr. Kingsbury that he was not passing any urine. He was catheterized and 8 cc urine were recovered. He was immediately hospitalized. The cause of anuria was thought to be due to massive doses of vitamin D, acute nephritis secondary to gastro-enteritis, and sulfadiazine.

The patient was ill but in no pain. His tongue was coated. His heart and lungs were within normal limits. The abdomen was tender throughout but otherwise not remarkable. The temperature was 100, the pulse 90 and respirations 24. The blood pressure was 90/55, nonprotein nitrogen 175 mg. per cent, carbon dioxide combining power 48.5 volumes per cent, creatinine 9.3 mg. per cent, blood sulfadiazine level 3.9 mg. per cent, hemoglobin 11 gm., red blood count 3,530,000, white blood count 12,200, 95 per cent polymorphonuclear leucocytes. The clotting time was 4½ minutes. The patient was catheterized but no urine recovered. An x-ray of the chest revealed no abnormalities.

Cystoscopy showed an absolutely dry bladder. Catheters were passed to each kidney without obstruction and no specimens of urine obtained. The pelves were washed but no sulfonamide crystals were found in the washings. An original roentgenogram with catheters in place revealed no abnormality.

We were thus confronted by nonobstructive anuria of conjectural origin. The patient had had large doses of vitamin D which it was thought might have produced renal damage inasmuch as he was not known to have had any renal disease previously. Further, it was supposed that the small doses of sulfadiazine touched off a fuse producing the explosion of anuria. We therefore decided to do a bilateral decapsulation which was done simultaneously under ether anesthesia on the day of admission. At the time it was noted that the kidneys did not bulge out of the capsule, contrary to the usual custom in other instances of sulfonamide block where decapsulation had been successful in relieving anuria. Furthermore, the dressings did not immediately become wet after operation. The first day fluids were maintained by intravenous 5 per cent glucose in distilled water (total 1500 cc). Morphine was given for postoperative pain and was continued at intervals for several weeks.

The day after operation the patient had hiccoughs. The maximum temperature was 99.4°. The nonprotein nitrogen remained the same but the creatinine rose to 11.6 mg. per cent. The blood pressure was 110/80. The red blood count and hemoglobin dropped and the white count rose. Practically no urine rewarded our efforts. The fluid intake on this day was 1670 cc, part of which was in the form of plasma and whole blood, (patient type O, Rh+) and 5 per cent glucose in distilled water. Aminophylin was given. CO_2 and O_2 inhalations were used, with indifferent success, for hiccoughs.

On the third hospital day the patient was drowsy, his abdomen distended, and the dressings only very slightly moist. No urine was obtained. The nonprotein nitrogen rose to 187 mg. per cent, the creatinine to 14.4 mg. per cent. CO_2 combining power was 50 volumes per cent, and plasma potassium 12 mg. per cent. The fluid intake was 1020 cc. The output was still zero. Consultation was held with Drs. J. A. MacDonald, W. D. Gatch and J. E. Owen, and in light of the patient's critical condition and failure to excrete urine we decided to institute peritoneal irrigation. At 11:00 p.m. under local anesthesia Dr. Owen inserted a Duke's trocar in the right lateral abdomen at the level of the umbilicus, and a Poole (sump) tube in the left lateral abdomen at a level just below the umbilicus. Because of the difficulty and time required in preparing Tyrode's solution, the irrigation was not started until the next morning.

On the fourth hospital day irrigation was started at the rate of 50 drops per minute. Suction was supplied to the exhaust tube on the left by a Stedman pump and the irrigating solution collected in a 5 gallon Wolfe bottle. The intake fluid was kept in two 6 litre pyrex Florence flasks about 2 feet above the patient. A Berkfeld filter was not used. The inlet tube, just distal to the patient, was warmed by jacketing with a series of hot water bottles. No difficulty was experienced with the inlet, but the clinical notes are replete with comments about difficulty in maintaining outflow due to clogging of the sump drain during the

first day or two. There was considerable leaking during this time around the outflow. Due to our unfamiliarity with the procedure, sufficient accuracy was not observed in maintaining quantitative records of inflow and outflow. After a day or so no further trouble was experienced with the outflow. On the fourth hospital day (the first day of dialysis) the nonprotein nitrogen was 185 mg. per cent, the creatinine 15 mg. per cent, the blood sulfadiazine level 3 mg. per cent, the blood serum sodium 329 mg. per cent, calcium 9.8 mg. per cent, serum protein 5, and hematocrit 29. The temperature was normal, the blood pressure 110/80, the urine output 0. There was no pain, the abdomen remained distended, and hiccoughs continued. Management consisted of caffeine, morphine, liquid diet, and Watkins enema.

On the fifth hospital day (second of dialysis) the patient complained of gas pains and was mentally confused. The dressings over the kidney incisions (previously dry) were moist, and there was copious leakage from around the exhaust tube. The nonprotein nitrogen rose to 192 mg. per cent, the blood urea clearance was 2 per cent, the serum protein 5.44 (A.G. ratio 1–1), cholesterol 203 mg. per cent, plasma chlorides 5.6 mg. per cent, calcium 9.7 mg. per cent, sulfadiazine level 2.9 mg. per cent, and hematocrit 31. The blood pressure was 140/60, temperature normal, urinary output zero. The fluid intake was maintained by intravenous 5 per cent glucose in distilled water and small amounts of normal saline, totaling 2000 cc. Enemata were continued for distention, as well as a colon tube, with fair results. The peritoneal exhaust fluid contained protein 0.062 mg. per cent, nonprotein nitrogen 61 mg. per cent, and E. coli was found in its culture.

On the sixth hospital day (third of dialysis) the face became edematous, the patient lethargic, and muscular twitching developed. The kidney incisions were quite moist. The nonprotein nitrogen was 165 mg. per cent, creatinine 14 mg. per cent, CO_2 34 vol. per cent, and blood sulfadiazine level 2 mg. per cent. The hematocrit was 30. The intake was 2000 cc intravenously, 5 per cent glucose in distilled water, and 1/6 molar sodium lactate to comabt acidosis. The temperature was 99.4, the blood pressure 120/70. Three cubic centimeters of urine were recovered. The peritoneal outflow was 23 litres. This outflow contained 2 gm. of protein, 77.3 mg. per cent of nonprotein nitrogen (17 gm. total) 88 mg. per cent of urea (19 gm. total) sulfadiazine level 1.03 mg. per cent, and its urea clearance test was 23 per cent.

The seventh hospital day (fourth of dialysis) found the patient's clinical condition unchanged. However, his nonprotein nitrogen was down to 125 mg. per cent, creatinine 11. mg. per cent, and blood sulfadiazine level 1.2 mg. per cent. Plasma chlorides were 599 mg. per cent, CO_2 31 vol. per cent. The fluid intake was 2250 cc, 1500 cc of which was intravenous 1/6 molar sodium lactate for acidosis. The temperature was normal, the blood pressure 170/80. A mild secondary anemia prevailed and the white blood count was 15,100. The peritoneal outflow was 16 litres. It contained E. coli and non-hemolytic streptococci. On this day, the ninth of anuria, 35 cc of urine were excreted, which

meagre though it was quantitatively, was a veritable qualitative Niagara. The 16 hour peritoneal outflow contained 0.06 protein (10 gm.), nonprotein nitrogen 47 mg. per cent (7 gm.), 0.8 mg. per cent of sulfadiazine.

On the eighth hospital day (fifth of dialysis) the patient became more alert and took sips of fluid orally. He was nauseated, had distention and severe abdominal pain. Peritonitis was feared so the penicillin in the Tyrode's solution was augmented by giving 100,000 units every 6 hours into the peritoneal intake tube, and penicillin was started intramuscularly and intravenously. Gastric drainage with suction was started. The nonprotein nitrogen fell to 90 mg. per cent, the blood sulfadiazine level to 1 mg. per cent, and the CO_2 rose to 41 vol. per cent. The fluid intake was 2000 cc (1500 cc of which was $\frac{1}{6}$ molar sodium lactate). The temperature was 100, the blood pressure 150/80. Urinalysis showed a large amount of albumin, 25 white blood cells, 10 red blood cells per 4 mm. field, bacteria and no casts. It contained 24 mg. per cent of urea, 7 gm. of NaCl per litre, and 3.1 mg. per cent of sulfadiazine. The peritoneal exhaust totaled 38 litres. A 6 hour 22 litre portion of this contained 0.073 mg. per cent (16. gm. total) protein, nonprotein nitrogen 34.1 mg. per cent, (7 gm. total) and 0.5 mg. per cent sulfadiazine.

Distention, edema and abdominal pain were the order of the ninth hospital day. Penicillin was complemented by streptomycin, 3 gm. daily, which was continued for 1 week in decreasing amounts. Digitalis and aminophylin were given. Sodium lactate and 5 per cent glucose were continued, intake totaling 1500 cc. The peritoneal output was 33.6 litres, (urea clearance 15 per cent, 11 cc, urea 36. mg. per cent). The gastric output 1400 cc and the urinary output 86 cc. The maximum temperature was 99.4, blood pressure 170/80. The nonprotein nitrogen went down to 62 mg. per cent. The blood sulfadiazine level was 0.8 mg. per cent, the blood sugar was 198 mg. per cent, plasma chlorides 673 mg. per cent, protein 5 (1–1 AG ratio). The CO_2 was 42 vol. per cent, the urine urea was 18 mg. per cent, the urine sulfadiazine 1.9 mg. per cent, and urine chlorides 7.5 gm. per litre. The patient was seen this day by Dr. Rubin Flocks, who was visiting in the city, and from him we received valuable information concerning his unpublished experiences with peritoneal irrigation.

The next day (seventh of dialysis) the clinical condition was unaltered. The nonprotein nitrogen was 66 mg. per cent, creatinine 5.9 mg. per cent, urea clearance 0.6 per cent. The urine urea was 72 mg. per cent. The urinary output rose to 295 cc. The peritoneal output was 31 litres, Levine suction 475 cc.

On the eleventh hospital day (eighth of dialysis) the nonprotein nitrogen was 65.7 mg. per cent, CO_2 was 30 vol. per cent. The intake consisted solely of 250 cc of whole blood. The urinary output was 730 cc. The blood pressure and temperature were unaltered. The peritoneal outflow was 34 litres.

On the twelfth day (ninth and last day of dialysis) the patient became overwhelmed with the complexity of his treatment and extracted both peritoneal tubes and the Levine the next day. He failed to notice his indwelling catheter which he left in as an unobtrusive nuisance. His temperature rose to 101, his

urinary output to 1400 cc. Intravenous sodium lactate and whole blood (250 cc) were given. The urine urea was 15 mg. per cent. The urinalysis showed a specific gravity of 1.012 and 0.5 per cent albumin.

On the thirteenth hospital day there was less edema. The nonprotein nitrogen rose to 76 mg. per cent and the creatinine to 8.1 mg. per cent. The urea clearance test was 3.7 per cent of normal. The urinary output increased to 2880 cc. The urinary sulfadiazine was less than 0.5 mg. per cent. The urinary urea was 186 mg. per cent. A transfusion was given and the sodium lactate continued.

The edema and abdominal distention decreased on the fourteenth hospital day but our fears were re-awakened because of the rise of the nonprotein nitrogen to 109 mg. per cent, in spite of an increased urinary output to 3990 cc. Plasma chlorides were 754 mg. per cent and CO_2 combining power was 27 vol. per cent. The acidosis was corrected by sodium lactate. The urine urea was 15 mg. per cent, and the specific gravity 1.008. Vitamins (B complex and C) were started in adequate dosage parenterally.

The following day the nonprotein nitrogen was 136 mg. per cent but the urea clearance test was better, 7.4 per cent of normal. The CO_2 was 42 vol. per cent. The urinary output was 3570 cc, containing 384 mg. per cent of urea. Five hundred cubic centimeters of whole blood were given and soft diet continued.

The sixteenth hospital day found a still higher nonprotein nitrogen 163 mg. per cent and CO_2 of 50 vol. per cent. The output was 3740 cc. Two hundred and fifty cubic centimeters of whole blood and intravenous sodium lactate, and 10 per cent glucose were administered. The temperature rose to 100.4 and blood pressure 195/90.

The succeeding 2 days (the seventeenth to the nineteenth) the nonprotein nitrogen remained the same and the patient was nauseated and distended and complaining of abdominal pain. He had his eighth and last blood transfusion. The creatinine rose again to 10.4 mg. per cent, the urea clearance test was 6.7 per cent of normal. The urine urea was now 600 mg. per cent, and its maximum specific gravity (1.014) attained. The temperature was 99°, the urinary output between 1500 cc and 3000 cc per 24 hours.

On the twentieth day the nonprotein nitrogen started down (141 mg. per cent) and a Levine tube was replaced for feeding with a high caloric mixture for 5 days. The latter was tolerated poorly, the patient vomiting a little every day for the remainder of his life. Hiccoughs persisted.

From the twenty-first to the thirty-third day the nonprotein nitrogen reduced to 100 mg. per cent and creatinine to 6.9 mg. per cent. The urea clearance test varied between 5.4 and 6.0 per cent of normal. The specific gravity reached its lowest, 1.002. The urinary output ranged from 1200 to 4500 cc per 24 hours. On the twenty-eighth day the patient sat up, and the next day he was absolutely comfortable and did not vomit. On the thirty-second day the catheter was removed for the first time. The patient had only 30 cc residual urine.

On the thirty-third day the temperature suddenly ascended to 101.8° (its highest since the first day) and the catheter was replaced. The temperature then returned to normal where it remained. From this day to the forty-third and last

day the nonprotein nitrogen gradually reascended to 194 mg. per cent, the output declined to 575 cc and then rose to 1100 cc. A marked secondary anemia developed and the white blood count went to 42,000 (97 per cent polymorphonuclears) and remained very high. A mass developed in the right upper quadrant and it was thought that a subdiaphragmatic abscess had developed. Paracentesis failed to verify this. Muscular twitching developed, the patient became cyanotic and incoherent. Later the pulse became irregular and fast (105). On the forty-second day respirations were fast and labored, of Cheyne-Stokes type, the neck rigid, edema recurred and the patient lost consciousness. During the last 11 days fluids were maintained intravenously. He expired on the forty-third day, January 8, 1947. Necropsy was permitted. At the time of death all incisions were healed.

The autopsy showed myocardial degeneration, slight pericardial effusion, bilateral pleural effusion, hypostatic pneumonia, adhesions between liver and diaphragm (no abscess), a small encapsulated mesenteric abscess (gram negative bacillus and positive coccus) in the upper abdomen; no generalized peritonitis; small pelvic abscess (gram negative bacillus) between the mesentery of the ileum and the sigmoid; a small encapsulated abscess (gram negative bacillus and coccus) of the left lobe of the prostate, and nephrosclerosis. The omentum was stretched tightly over the viscera and was uninflamed. The peritoneum and omentum were smooth. The intestines were bound together by a small number of thin filmy adhesions. The renal parenchyma cut with increased resistance. The cortex showed a marked thin scarring. The medulla appeared normal. The pelves were normal. Histologically the kidneys were as follows: the glomeruli were normal in number, somewhat edematous, and the capillary tufts were normal. The tubules in the cortex and medulla showed marked degeneration of the lining epithelium with increased connective tissue. The tubular channels were full of casts though none were ever found in the urine. The vascular channels showed only moderate degenerative thickening of their walls.

COMMENT

A case of anuria of uncertain origin has been related in which it was hoped that the renal lesion was reversible due to a combination effect of vitamin D and sulfonamide toxicity. Peritoneal dialysis was therefore undertaken after decapsulation appeared to have failed. We were unable to maintain as rapid rate of flow, as recommended by Fine. Nevertheless, in the face of impending renal disaster, the treatment demonstrated that it was possible to reduce the chemical evidences of uremia while it was used. During this period the kidneys regained their excretory ability, normal so far as water is concerned and inadequate so far as dissolved substances are concerned. The blood and peritoneal irrigation urea clearance did not attain the degree of efficiency accomplished by Fine and others. Our difficulty in maintaining a high enough rate of flow was imperfection in the exhaust system in the patient's abdomen although a sump drain was used. We used no sulfadiazine in our fluid for obvious reasons. We also found difficulty, not insurmountable, in controlling acidosis. The method

did not cause protein deficit although no protein was used in the irrigating fluid. Frequent transfusions and some plasma were given.

The procedure was terminated on its ninth day by the sudden removal of tubes by the patient. At the time, however, enough urine was being excreted and the nonprotein nitrogen was low enough (62) so that we hoped the kidneys would be able to handle their load. During the period of dialysis, sulfadiazine disappeared from the blood stream, both via the peritoneal irrigating fluid and the urine. However, upon discontinuing peritoneal lavage, there was an immediate rise of nonprotein nitrogen although the water excreting ability of the kidneys continued to improve. When the chemical evidences of uremia had recurred almost to the level preceding dialysis, they again began to subside and all concerned thought the patient was going to recover. Then, coincidental with removal of the previously continuously anchored catheter, uremia recurred a third and last time terminating in death on the forty-fifth day since onset of anuria. It is possible that longer use of dialysis and more rapid flow would have altered the ultimate outcome. Too much emphasis cannot be placed on the complexity of the method, the need of exhausitive laboratory studies, and of detailed coordinated team work between clinician, nurse, laboratory, pharmacy and house staff. The method is expensive in a private hospital where one has to consider the cost of laboratory studies, preparation and sterilization of fluid, drugs, and private nursing (which is essential). Nevertheless, we commend its use in nonobstructive anuria, particularly if the renal failure may be reversible. Autopsy of our patient showed that the peritoneum withstood the treatment satisfactorily and that the renal lesion was tubular degeneration with intact glomeruli.

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DISCUSSION

DR. BENJAMIN S. BARRINGER (New York, N. Y.): I suppose that we are liable under the law if we do a double vasotomy.

PRESIDENT O'CROWLEY: That is a remedial measure.

DR. BARRINGER: Is it, or is it not? I don't see why you can't be sued for that.

DR. JOHN K. ORMOND (Detroit, Mich.): We have had recently two experiences with this peritoneal lavage. We didn't have the same success getting as much fluid through as Dr. Wishard did, nor did we have the same success in keeping the patient alive as long, nor were we able to cause any increase in the amount of urine, but I think that the results show what can be done. Case 1 was a young doctor who had taken only 60 gr. of sulfadiazine and immediately became anuric. We allowed him to go 4 or 5 days before doing anything unusual, and then established this type of drainage. You can see the amount of fluid we were able to get through on the various days.

(Slide) This shows what his NPN was doing, and then what happened to the NPN. The first day of perfusion it was 150. It fell to 146, then to 125, then went up to 145, and that was due to the fact we had trouble with getting the solution through on that particular day; then it fell to 119, in spite of which he died. This shows the amount of NPN taken out with the perfusion fluid.

Urea clearance was done on the fluid from the patient, and it shows here with the maximum clearance 24.8, when we had a large amount go through, and with a smaller amount, fell to 6.7 gm.

Case I. Amount of perfusion fluid	
4/15/47	8,000 cc
4/16/47	12,500 cc
4/17/47	9,500 cc
4/18/47	8,000 cc

Case II. Amount of perfusion fluid	
5/2/47	2,700 cc
5/3/47	10,000 cc
5/4/47	9,900 cc
5/5/47	8,300 cc
5/6/47	2,600 cc

Case I

ADM.	BLOOD			PERFUSION FLUID NPN
	NPN	CO_2	CL	
4/8	38			
4/10	74	52.2		
4/12	106	48.3	467	
4/14	127	51.3		
Perfusion Started				
4/15	150	A.M.	413	64.5
	146	P.M.		131
4/16	125	35.9	453	
4/17	145	44.4	473	125
4/18	119	52.8	460	91.2

Case II

ADM.	BLOOD			PERFUSION FLUID NPN
	NPN	CO_2	CL	
4/30	103	45.5		
5/1	115			
5/2	165	70.5	333	
Perfusion Started				
5/3	115	58	390	A.M. 88
				P.M. 115
5/4	100	63.2	400	68
5/5	194	52.6	427	84
5/6	135			83

(Slide) This was a colored woman who came in with anuria. This shows the amount of fluid we were able to get through with her. It is a difficult situation.

(Slide) This shows the NPN as it behaved, the CO_2 and the NPN of the fluid itself.

We had autopsies in both these patients, and we didn't find any sign of peritonitis. However, the peritoneum in both cases was somewhat thickened and opaque, and we got the idea that while this may be a very effective method to tide the patient over a short period, that eventually the peritoneum becomes more or less impervious and will not be able to act as a permeable membrane.

Dr. John B. Wear (Madison, Wis.): I should like to compliment Dr. Wishard on his very exhaustive review of this whole subject. He also apparently had a very exhausting patient both to him and his confreres. The work involved was tremendous.

In 1935 we began on peritoneal lavage by doing a number of dogs first. In reviewing the literature we found several references by the Germans to the peritoneum as a dialyzing and absorbing membrane. We could find no one who had used it as a real lavage for the relief of anuria.

As our first case, we used a man who had both ureters obstructed by carcinoma of the bladder and whose death was imminent. Without great difficulty, we removed 11 gm. of nonprotein nitrogen. We then went on and did several other cases. We had one case very similar to the one reported today in that urinary excretion was copious and everything looked as if we were over the hump and then suddenly he died in a day or two. This has happened, I am sure, to all of us in cases of anuria with and without peritoneal lavage.

Uremia is an interesting subject and the last word has not been said by any means. We gave up peritoneal lavage because the removal of nonprotein nitrogen did not seem to be the basic factor. The phenols, amino acids and toxic products in the intestinal tract will have to be attacked as well. I have long thought that if we could irrigate the entire intestinal tract along with peritoneal lavage, recovery would be more likely.

We had very little trouble in getting the fluid through the abdominal cavity. A small metal trocar was used at the inlet site and a bladder trocar with holes cut in the side was used at the outlet site. This worked rather well and as high as 33,000 cc of fluid was used in 8 hours. One patient we did on three different occasions, and on death autopsy showed no sign of peritonitis. That was before the days of sulfa drugs and penicillin. If one uses the lavage for as long as Dr. Wishard did, these drugs would likely be of some help.

In the beginning of the lavage the NPN of the blood may not fall as the tissues are saturated and this excess has to be removed as well as the nonprotein nitrogen that continues to collect as a result of the renal dysfunction. There is no question that huge amounts of nonprotein nitrogen can be removed by peritoneal lavage.

There may be some fluid retained and this has to be watched if we would avoid drowning the patient. The peritoneum is a good absorbing medium. The procedure is safe but entails much work. We became discouraged, as the

more we studied uremia the more convinced we became that we were not fighting fundamental factors and had the buggy in front of the horse.

DR. VINCENT J. O'CONOR (Chicago, Ill.): In answer to Dr. Barringer's question, the point that I raised was that except for the states enumerated—Illinois, Florida, and I think Massachusetts are not included; New York State is not included. Vasotomy is illegal, with the one provision subject to interpretation: "except in in its relationship to medical treatment." That means if you can go before a jury and prove that epididymitis has a certain mortality in prostatic disease, which would result if the vasa were not ligated, then you might be justified before the court and the jury to have performed the procedure. That might also be proved in the case of a patient who comes to you with recurrent nonspecific bilateral epididymitis in whom you would recommend a vas resection on either side to prevent further recurrence, as we know it frequently does. However, we are still on an absolutely unknown legal basis as far as using our individual judgment and the old legal phrase of *res ipsa loquiter*, the thing speaking for itself, determines the actual legal aspect of the problem.

I would like very briefly to discuss Dr. Wishard's paper. My experience with peritoneal lavage has been largely that of the mechanic in the picture. Dr. Marquart, a medical man in our institution, became interested in this problem 2 years ago but couldn't get the general surgeons interested. So he spoke to us, and we said we would be very glad to cooperate with him, although our cooperation eventually was limited to putting the tubes in. He had a grant by which he could run the laboratory work. He had a team, and the Baxter people provided the material, which is no inconsequential item in these cases.

In the first 3 patients on whom I did the mechanical work, we put a Pezzer catheter in the left upper abdominal quadrant. We put an elbow catheter with a metal tube in the lower right abdominal quadrant.

John Wear says it is not a complicated procedure. We thought it was a very complicated procedure with the different techniques to even get proper peritoneal drainage. The omentum will wrap itself around these tubes, even with a constant flow.

I only mention this experience because we can throw a little more optimistic shadow on the thing than has been given here today.

Of the first 3 patients that we did this on, 2 were definitely irreversible cases of renal damage, and it was done with the idea of testing our technique, and so forth. The amount of reduction of the NPN and the improvement for 3 or 4 days in the ability of these patients to eat, cessation of their headaches, and so forth, was very striking even though they all went on and died within a very short time.

The fourth patient was a girl who had a transfusion reaction, who was definitely dying, in our opinion. She was treated conservatively for the maximum length of time, and then she was put on peritoneal lavage for 10 days and recovered. Whether or not she might have recovered without the peritoneal lavage—I mean the imponderables in this subject, we don't know. It seemed to us as though her life was saved by this procedure.

Peritonitis was a factor in the fifth case. The patient died of peritonitis, even though she was receiving penicillin and sulfonamides, even though penicillin was being added to the irrigation solution. We thought this patient would have gotten well, and the pathologists thought so, too, if peritonitis hadn't intervened.

The next patient had a sulfonamide reaction. The kidneys had been decapsulated elsewhere, rough decapsulation, the type sometimes that is followed by relief of the oliguria in these cases, but no urine had been secreted for 12 days. This patient recovered after 11 days of peritoneal lavage. I am told, however, that the renal function and the evidence of damage in this last patient gives a very pessimistic outlook for future life.

At present peritoneal lavage entails so much detailed attention and hospital teamwork that its application must of necessity be limited to a teaching hospital which has the necessary equipment and trained laboratory personnel. The expense for the average patient would be prohibitive unless the work is done under a special fund or research grant.

DR. JOHN K. ORMOND (Detroit, Mich.): I have nothing further to say regarding the cases I reported, but I would like to mention the edema of which Dr. Wear spoke. We thought in our first case we were able to lessen the pulmonary edema by perfusing with a hypertonic solution.

DR. WILLIAM P. HERBST (Washington, D. C.): These cases were presented as a matter of informative record. We are not enthusiastic about the clinical response, but in view of the fact that we are more or less searching for all aids possible in assisting these hopeless advanced cases, it proves an opportunity to learn something of value in the further control of malignancy.

I thought, considering Dr. Davis' cases, that there may have been something a little suggestive about the experience that Dr. Bagley had with bladder tumor cases. It seemed as though the responses that seemed to be really favorable were in the cases of bladder tumor, whereas there was no variation in the general clinical course in the other types of malignancy.

One case which he didn't have an opportunity to describe happened to be a hypernephroma which was attached to the descending colon, and the kidney was removed without interfering with the lumen of the bowel, and this man was suffering from acute pain which needed opiates to control.

Following the administration of inositol in that particular instance, his pain was relieved and he didn't need opiates. We are looking forward to using some of it intravenously when that is provided.

DR. WILLIAM NILES WISHARD, JR. (Indianapolis, Ind.): I would merely like to thank the men who commented on the subject of peritoneal irrigation. I would have liked to have asked Dr. O'Conor if any of those 55 spontaneous regenerations of the vas made any mention of any postoperative complications. One of them I know did have. The tie came out. There was a massive hemorrhage and the continuity of that vas was established and the wife became pregnant.

Concerning Dr. Ormond's case, we had a patient about eight years ago who had an anuria from extra-urinary pressure on both ureters due to a low-lying re-

troperitoneal sarcoma, which was relieved by catheter drainage, and subsequently x-ray therapy, but, unfortunately, the patient had a habit of pulling out his catheters and we had to cystoscope him so many times, he became infected and he died on the fourteenth day of septicemia.

There has been mention, I think, in almost every patient who has had peritoneal lavage and recovered, that there had been permanent evidence of decided renal damage, as evidenced by lowered urea clearance tests.

PRESIDENT O'CROWLEY: Gentlemen, previous to this meeting, one of our members, Dr. McClelland, requested that a visiting surgeon to this country, and a friend of his, be allowed to come here and sit in this meeting, and it was granted. This gentleman, a urologist, teaching urology in the University of Sheffield, England, is visiting this country and the clinics in this country. He is a Scotchman. His name is Mr. J. C. Anderson. He wishes to give an appreciative word to you.

MR. J. C. ANDERSON: I do not want to trespass upon your time unnecessarily, but I would like to thank you for the great privilege that you have conferred upon me in allowing me to attend this meeting, which is a meeting of the premiere urological association in the world.

In England, we have been very slow to divorce the specialties from general surgery, and urology is the last one to undergo this process, and it is happening at the present moment. If anything was needed to convince me of the necessity for urology to be practiced by urologists and not by general surgeons, it is what I have heard and seen at this meeting. Their approach to the subject is quite inadequate.

I also would like to take this opportunity of thanking the members of my own profession who have welcomed me to the clinics. So many of them are here today, and I would like them to know how much I have appreciated their kindness, and to let them know how much I have learned during these visits. I would also like to pay a tribute to the ordinary man and woman in the street of this country, because I have experienced nothing but courtesy and kindness from all sections of this country. This is my first visit to this country. In brief, I would like to tell you the tremendous impression that this visit has made upon me. I hardly think the education of any specialist in Europe is complete without a visit to this side of the Atlantic. I have been most impressed by the virility of the people, by their energy, by their achievements of this and former generations in retaining wild nature; I have been impressed by the wealth and power of the country. The exercise of power carries with it certain duties to the rest of mankind, and I know that this country is equal to it.

Gentlemen, you have a great heritage, and you have a great destiny. I thank you very much indeed.

PRESIDENT O'CROWLEY: Before I adjourn this meeting, I wish again to tell you my great appreciation for having been placed in this office, the highest honor that any urologist can have. I want to thank you all for the grand cooperation you gave me in making this a very good meeting, and I hope that we will all be together next year.